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=> e philipp mario t/au

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E2 13 PHILIPP MARIO/AU  
E3 72 --> PHILIPP MARIO T/AU  
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=> s e2-e3 and borrel?

L1 63 ("PHILIPP MARIO"/AU OR "PHILIPP MARIO T"/AU) AND BORREL?

=> dup rem l1

PROCESSING COMPLETED FOR L1

L2 42 DUP REM L1 (21 DUPLICATES REMOVED)

=> d bib ab 1-

YOU HAVE REQUESTED DATA FROM 42 ANSWERS - CONTINUE? Y/(N):y

L2 ANSWER 1 OF 42 MEDLINE

AN 2002119970 IN-PROCESS

DN 21843453 PubMed ID: 11854355

TI An immune evasion mechanism for spirochetal persistence in lyme

\*\*\*borreliosis\*\*\*

AU Liang Fang Ting; Jacobs Mary B; Bowers Lisa C; \*\*\*Philipp Mario T\*\*\*

CS Department of Parasitology, Tulane Regional Primate Research Center,  
Tulane University Health Sciences Center, Covington, LA 70433.

SO JOURNAL OF EXPERIMENTAL MEDICINE, (2002 Feb 18) 195 (4) 415-22.

Journal code: 2985109R. ISSN: 0022-1007.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS IN-PROCESS; NONINDEXED; Priority Journals

ED Entered STN: 20020221

Last Updated on STN: 20020221

AB \*\*\*Borrelia\*\*\* burgdorferi, the Lyme disease spirochete, persistently  
infects mammalian hosts despite the development of strong humoral  
responses directed against the pathogen. Here we describe a novel  
mechanism of immune evasion by *B. burgdorferi*. In immunocompetent mice,  
spirochetes that did not express ospC (the outer-surface protein C gene)  
were selected within 17 d after inoculation, concomitantly with the  
emergence of anti-OspC antibody. Spirochetes with no detectable OspC  
transcript that were isolated from immunocompetent mice reexpressed ospC  
after they were either cultured in vitro or transplanted to naive  
immunocompetent mice, but not in OspC-immunized mice. *B. burgdorferi*  
persistently expressed ospC in severe combined immune-deficient (SCID)  
mice. Passive immunization of *B. burgdorferi*-infected SCID mice with an  
anti-OspC monoclonal antibody selectively eliminated ospC-expressing  
spirochetes but did not clear the infection. OspC-expressing spirochetes  
reappeared in SCID mice after the anti-OspC antibody was eliminated. We

09445803

submit that selection of surface-antigen nonexpressers is an immune evasion mechanism that contributes to spirochetal persistence.

L2 ANSWER 2 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2001:553356 BIOSIS

DN PREV200100553356

TI Transcriptional regulation in spirochetes of medical importance.

AU Indest, Karl J. (1); Ramamoorthy, Ramesh (1); \*\*\*Philipp, Mario T.\*\*\*  
\*\*\* (1)\*\*\*

CS (1) Department of Parasitology, Tulane Regional Primate Research Center,  
Tulane University Medical Center, 18703 Three Rivers Road, Covington, LA,  
70433 USA

SO Saier, Milton H., Jr. [Editor]; Garcia-Lara, Jorge [Editor]. JMMB  
Symposium Series, (2001) No. 3, pp. 159-169. JMMB Symposium Series. The  
spirochetes: Molecular and cellular biology. print.  
Publisher: Horizon Scientific Press 32 Hewitts Lane, Wymondham, Norfolk,  
NR18 0JA, UK.  
ISBN: 1-898486-27-1 (cloth).

DT Book

LA English

SL English

L2 ANSWER 3 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

1

AN 2001:543238 BIOSIS

DN PREV200100543238

TI Analysis of \*\*\*Borrelia\*\*\* burgdorferi vlsE gene expression and  
recombination in the tick vector.

AU Indest, Karl J.; Howell, Jerrilyn K.; Jacobs, Mary B.; Scholl-Meeker,  
Dorothy; Norris, Steven J.; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Tulane Regional Primate Research Center, Tulane University Health  
Sciences Center, 18703 Three Rivers Rd., Covington, LA, 70433:  
philipp@tpc.tulane.edu USA

SO Infection and Immunity, (November, 2001) Vol. 69, No. 11, pp. 7083-7090.  
print.

ISSN: 0019-9567.

DT Article

LA English

SL English

AB Expression and recombination of the antigenic variation vlsE gene of the  
Lyme disease spirochete \*\*\*Borrelia\*\*\* burgdorferi were analyzed in  
the tick vector. To assess vlsE expression, Ixodes scapularis nymphs  
infected with the B. burgdorferi strain B31 were fed on mice for 48 or 96  
h or to repletion and then crushed and acetone fixed either immediately  
thereafter (ticks collected at the two earlier time points) or 4 days  
after repletion. Unfed nymphs also were examined. At all of the time  
points investigated, spirochetes were able to bind a rabbit antibody  
raised against the conserved invariable region 6 of VlsE, as assessed by  
indirect immunofluorescence, but not preimmune serum from the same rabbit.  
This same antibody also bound to B31 spirochetes cultivated in vitro.

Intensity of fluorescence appeared highest in cultured spirochetes,  
followed by spirochetes present in unfed ticks. Only a dim fluorescent  
signal was observed on spirochetes at the 48 and 96 h time points and at  
day 4 postrepletion. Expression of vlsE in vitro was affected by a rise in  
pH from 7.0 to 8.0 at 34degreeC. Hence, vlsE expression appears to be

sensitive to environmental cues of the type found in the *B. burgdorferi* natural history. To assess vlsE recombination, nymphs were capillary fed the *B. burgdorferi* B31 clonal isolate 5A3. Ticks thus infected were either left to rest for 4 weeks (Group I) or fed to repletion on a mouse (Group II). The contents of each tick from both groups were cultured and 10 *B. burgdorferi* clones from the spirochetal isolate of each tick were obtained. The vlsE cassettes from several of these clones were amplified by PCR and sequenced. Regardless of whether the isolate was derived from Group I or Group II ticks, no changes were observed in the vlsE sequence. In contrast, vlsE cassettes amplified from *B. burgdorferi* clones derived from a mouse that was infected with B31-5A3 capillary-fed nymphs showed considerable recombination. It follows that vlsE recombination does not occur in the tick vector.

L2 ANSWER 4 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2001:527295 BIOSIS

DN PREV200100527295

TI Characterization of a \*\*\**Borrelia*\*\*\* *burgdorferi* VlsE invariable region useful in canine Lyme disease serodiagnosis by enzyme-linked immunosorbent assay.

AU Liang, Fang Ting; Jacobson, Richard H.; Straubinger, Reinhard K.; Grooters, Amy; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Tulane Regional Primate Research Center, Tulane University Health Sciences Center, 18703 Three Rivers Rd., Covington, LA, 70433:  
philipp@tpc.tulane.edu USA

SO Journal of Clinical Microbiology, (November, 2001) Vol. 38, No. 11, pp. 4160-4166. print.

ISSN: 0095-1137.

DT Article

LA English

SL English

AB Sera collected from dogs experimentally infected with \*\*\**Borrelia*\*\*\* *burgdorferi* by tick inoculation were analyzed for an antibody response to each of the six invariable regions (IRs; i.e., IR1 to IR6) of VlsE, the variable surface antigen of *B. burgdorferi*. Six synthetic peptides (C1 to C6), which reproduced the six IR sequences were used as peptide-based, enzyme-linked immunosorbent assay (ELISA) antigens. Two IRs, IR2 and IR6, were found to be immunodominant. Studies with serially collected serum samples from experimentally infected dogs revealed that the antibody response to IR6 appears earlier and is stronger than that to IR2. Thus, the IR6 sequence alone appeared to be sufficient for serodiagnosis. When C6 alone was used as antigen, the peptide-based ELISA was positive in 7 of 23 dogs (30%) as early as 3 weeks postinfection. All dogs (n = 33) became strongly positive 1 or 2 weeks later, and this response persisted for the entire study, which lasted for 69 weeks. Of 55 sera submitted by veterinarians from dogs suspected of having Lyme disease, 19 were also positive by the C6 ELISA, compared to 20 positives detected by immunoblot analysis using cultured *B. burgdorferi* lysates as antigen. The sensitivity of using C2 and C6 together for detecting specific antibody in both experimentally infected and clinically diagnosed dogs was not better than sensitivity with C6 alone, confirming that C6 suffices as a diagnostic probe. Moreover, the C6 ELISA yielded 100% specificity with serum samples collected from 70 healthy dogs, 14 dogs with infections other than *B. burgdorferi*, and 15 animals vaccinated with either outer surface protein A, whole-spirochete vaccines, or the common puppy-vaccines. Therefore,

this C6 ELISA was both sensitive and specific for the serodiagnosis of canine Lyme disease and could be used with vaccinated dogs.

L2 ANSWER 5 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

2

AN 2002:69169 BIOSIS

DN PREV200200069169

TI CD19+ cells produce IFN-gamma in mice infected with \*\*\*Borrelia\*\*\* burgdorferi.

AU Ganapamo, Frederic; Dennis, Vida A.; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Department of Parasitology, Tulane Regional Primate Research Center,  
18703 Three Rivers Road, Covington, LA, 70433: philipp@tpc.tulane.edu USA

SO European Journal of Immunology, (December, 2001) Vol. 31, No. 12, pp.  
3460-3468. <http://www.wiley-vch.de/vch/journals/2040/>. print.

ISSN: 0014-2980.

DT Article

LA English

AB We have recently shown that production of IFN-gamma and IL-10, but not IL-4 is specifically induced in the lymph nodes of C3H/HeJ (disease susceptible) and C57BL/6J (disease resistant) mice 1 week after infection with \*\*\*Borrelia\*\*\* burgdorferi spirochetes. The present study was conducted to determine the phenotypes of ex vivo lymph node cells obtained from infected mice of both strains at this time point. The percentages of CD3+, CD4+, CD8+, TCRalpha/beta+ and TCR gamma/delta+ cells decreased in both strains of mice compared to LN from naive mice. In contrast, there was a threefold increase in the proportion of CD19+ cells. In view of this expansion of the B cell proportion, we examined the ability of purified CD19+ cells and CD43+ cells to produce both IL-10 and IFN-gamma when the cells were restimulated in vitro with *B. burgdorferi* freeze-thawed spirochetes. As expected, CD43+ cells were able to produce both cytokines, but not IL-4. Surprisingly, CD19+ (B) cells also were able to produce IFN-gamma in comparable amounts, in addition to IL-10. Intracellular staining of CD19+ cells with anti-IFN-gamma antibody confirmed this finding. We discuss this novel phenomenon in terms of its possible underlying mechanisms and its relevance, both in the context of the immunology of Lyme disease and that of other infectious diseases.

L2 ANSWER 6 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

3

AN 2001:303019 BIOSIS

DN PREV200100303019

TI C-terminal invariable domain of VlsE is immunodominant but its antigenicity is scarcely conserved among strains of lyme disease spirochetes.

AU Liang, Fang Ting; Bowers, Lisa C.; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Tulane Regional Primate Research Center, Tulane University Health Sciences Center, 18703 Three Rivers Rd., Covington, LA, 70433:  
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SO Infection and Immunity, (May, 2001) Vol. 69, No. 5, pp. 3224-3231. print.  
ISSN: 0019-9567.

DT Article

LA English

SL English

AB VlsE, the variable surface antigen of \*\*\*Borrelia\*\*\* burgdorferi, contains two invariable domains located at the amino and carboxyl terminal

ends, respectively, and a central variable domain. In this study, both immunogenicity and antigenic conservation of the C-terminal invariant domain were assessed. Mouse antiserum to a 51-mer synthetic peptide (Ct) which reproduced the entire sequence of the C-terminal invariant domain of VlsE from *B. burgdorferi* strain B31 was reacted on immunoblots with whole-cell lysates extracted from spirochetes of 12 strains from the *B. burgdorferi* sensu lato species complex. The antiserum recognized only VlsE from strain B31, indicating that epitopes of this domain differed among these strains. When Ct was used as enzyme-linked immunosorbent assay (ELISA) antigen, all of the seven monkeys and six mice that were infected with B31 spirochetes produced a strong antibody response to this peptide, indicating that the C-terminal invariant domain is immunodominant. None of 12 monkeys and only 11 of 26 mice that were infected with strains other than B31 produced a detectable anti-Ct response, indicating a limited antigenic conservation of this domain among these strains. Twenty-six of 33 dogs that were experimentally infected by tick inoculation were positive by the Ct ELISA, while only 5 of 18 serum samples from dogs clinically diagnosed with Lyme disease contained detectable anti-Ct antibody. Fifty-seven of 64 serum specimens that were collected from American patients with Lyme disease were positive by the Ct ELISA, while only 12 of 21 European samples contained detectable anti-Ct antibody. In contrast, antibody to the more conserved invariant region IR6 of VlsE was present in all of these dog and human serum samples.

L2 ANSWER 7 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

4

AN 2001:187806 BIOSIS

DN PREV200100187806

TI C-terminal invariant domain of VlsE may not serve as target for protective immune response against \*\*\**Borrelia*\*\*\* *burgdorferi*.

AU Liang, Fant Ting; Jacobs, Mary B.; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Tulane Regional Primate Research Center, Tulane University Health Sciences Center, 18703 Three Rivers Rd., Covington, LA, 70433:  
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SO Infection and Immunity, (March, 2001) Vol. 69, No. 3, pp. 1337-1343.  
print.

ISSN: 0019-9567.

DT Article

LA English

SL English

AB VlsE, the variable surface antigen of the Lyme disease spirochete, \*\*\**Borrelia*\*\*\* *burgdorferi*, contains two invariant domains, at the amino and carboxyl termini, respectively, which collectively account for approximately one-half of the entire molecule's length and remain unchanged during antigenic variation. It is not known if these two invariant domains are exposed at the surface of either the antigen or the spirochete. If they are exposed at the spirochete's surface, they may elicit a protective immune response against *B. burgdorferi* and serve as vaccine candidates. In this study, a 51-mer synthetic peptide that reproduced the entire sequence of the C-terminal invariant domain of VlsE was conjugated to the carrier keyhole limpet hemocyanin and used to immunize mice. Generated mouse antibody was able to immunoprecipitate native VlsE extracted from cultured *B. burgdorferi* B31 spirochetes, indicating that the C-terminal invariant domain was exposed at the antigen's surface. However, this domain was inaccessible to antibody

binding at the surface of cultured intact spirochetes, as demonstrated by both an immunofluorescence experiment and an in vitro killing assay. Mouse antibody to the C-terminal invariable domain was not able to confer protection against *B. burgdorferi* infection, indicating that this domain was unlikely exposed at the spirochete's surface in vivo. We concluded that the C-terminal invariable domain was exposed at the antigen's surface but not at the surface of either cultured or in vivo spirochetes and thus cannot elicit protection against *B. burgdorferi* infection.

L2 ANSWER 8 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2001:222382 BIOSIS

DN PREV200100222382

TI \*\*\**Borrelia*\*\*\* *burgdorferi* stimulates in vitro a selective expansion of CD3-CD4-CD8- (triple negative) autoreactive cells in naive rhesus monkey lymphocytes.

AU Ganapamo, Frederic; Dennis, Vida A.; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Dept. of Parasitology, Tulane Regional Primate Research Center, Tulane University Health Sciences Center, 18703 Three Rivers Rd., Covington, LA, 70433: Philipp@tpc.tulane.edu USA

SO Journal of Infectious Diseases, (15 April, 2001) Vol. 183, No. 8, pp.

1221-1228, print.

ISSN: 0022-1899.

DT Article

LA English

SL English

AB Autoreactive cell lines were generated from cell suspensions of freshly isolated naive monkey lymph node (LN) cells and peripheral blood mononuclear cells by cocultivation with freeze-thawed \*\*\**Borrelia*\*\*\* *burgdorferi* spirochetes (Bb/FT). These cells produced interleukin (IL)-6 when cocultured with autologous antigen-presenting cells (APCs) alone without Bb/FT. IL-6 production was not observed when control cell lines were stimulated in the same fashion. CD4+-enriched T cell populations obtained from the LN autoreactive cell line also produced IL-6 when cultivated with APCs alone. When these cells were cultivated further in the presence of APCs, a population of cells whose phenotype was CD56+/-CD4-CD8-CD3- was predominantly selected. These cells both proliferated and produced IL-6 when cocultured with APCs alone. The possible relevance of these cells to Lyme disease pathogenesis remains to be determined.

L2 ANSWER 9 OF 42 CAPLUS COPYRIGHT 2002 ACS

AN 2001:766153 CAPLUS

TI Antibody response to IR6, a conserved immunodominant region of the VlsE lipoprotein, wanes rapidly after antibiotic treatment of \*\*\**Borrelia*\*\*\* *burgdorferi* infection in experimental animals and in humans

AU \*\*\*Philipp, Mario T.\*\*\* ; Bowers, Lisa C.; Fawcett, Paul T.; Jacobs, Mary B.; Liang, Fang Ting; Marques, Adriana R.; Mitchell, Paul D.; Purcell, Jeanette E.; Ratterree, Marion S.; Straubinger, Reinhard K.

CS Tulane Regional Primate Research Center, Tulane University Health Sciences Center, Covington, LA, 70433, USA

SO J. Infect. Dis. (2001), 184(7), 870-878

CODEN: JIDIAQ; ISSN: 0022-1899

PB University of Chicago Press

DT Journal

LA English

AB Invariable region (IR)6, an immunodominant conserved region of VlsE, the antigenic variation protein of \*\*\*Borrelia\*\*\* burgdorferi, is currently used for the serol. diagnosis of Lyme disease in humans and canines. A longitudinal assessment of anti-IR6 antibody levels in B. burgdorferi-infected rhesus monkeys revealed that this level diminished sharply after antibiotic treatment (within 25 wk). In contrast, antibody levels to P39 and to whole-cell antigen exts. of B. burgdorferi either remained unchanged or diminished less. A longitudinal anal. in dogs yielded similar results. In humans, the anti-IR6 antibody titer diminished by a factor of .gtoreq.4 in successfully treated patients and by a factor of <4 in treatment-resistant patients. This result suggests that the quantification of anti-IR6 antibody titer as a function of time should be investigated further as a test to assess response to Lyme disease therapy or to det. whether a B. burgdorferi infection has been eliminated.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2001:278537 BIOSIS

DN PREV200100278537

TI Differential cross regulation of IL-10, IFN-gamma and IL-4 production by ex vivo lymph node cells and short-term culture cell lines from \*\*\*Borrelia\*\*\* burgdorferi-infected Lyme-disease (LD)-resistant and susceptible mice.

AU Ganapamo, Frederic (1); Dennis, Vida A. (1); \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Tulane Regional Primate Center, 18703 Three Rivers Road, Covington, LA, 70433 USA

SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A305. print.

Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001

ISSN: 0892-6638.

DT Conference

LA English

SL English

AB Lymph node cells (LNC) from C3H/HeJ mice (C3H, LD susceptible) and C57 BL/6J mice (C57, disease resistant) infected for one week with B. burgdorferi strain JD1 produced IFN-gamma and IL-10 when stimulated in vitro with B. burgdorferi spirochetes (Bb). IL-4 secretion was undetectable. When cultured with neutralizing anti-IL-10 antibody, Bb-stimulated LNC from C57 produced higher levels of IFN-gamma than cells cultured with Bb alone. In contrast, no effect of IL-10 neutralization was observed on IFN-gamma production by cells from C3H. Anti-IFN-gamma antibody had no effect on the production of IL-10 by LNC from C57 but a decrease in IL-10 production was detected in supernatants of LNC from C3H. To study the effect of these cytokines on T-cell maturation, short-term cell lines were generated from LNC of infected mice in the presence of either anti-IL-10 or anti-IFN-gamma antibody. Cell lines from both strains produced IFN-gamma in the presence of APC alone; the presence of Bb + APC was required for IL-10 production. A significant up-regulation of IL-4 production was observed in cell lines from C3H (but not C57) generated in the presence of anti-IFN-gamma antibody. Together, these data suggest that IFN-gamma and IL-10 have different effects on the maturation of C3H and C57 T-cells. The inhibition by IFN-gamma of IL-4-producing T-cells in C3H

and the enhanced inhibition of IFN-gamma production by IL-10 in C57 lymphocytes could explain the differential susceptibility to LD of these two mouse strains.

L2 ANSWER 11 OF 42 CAPLUS COPYRIGHT 2002 ACS

AN 2000:772768 CAPLUS

DN 133:334034

TI VlsE-derived peptides, nucleic acids, and vaccines for diagnosis and prevention of lyme disease

IN \*\*\*Philipp, Mario T.\*\*\* ; Liang, Fang Ting

PA The Administrators of the Tulane Educational Fund, USA

SO PCT Int. Appl., 76 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2000065064 A1 20001102 WO 2000-US11085 20000425

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,  
CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,  
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CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1171605 A1 20020116 EP 2000-926350 20000425

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO

PRAI US 1999-300971 A2 19990428

WO 2000-US11085 W 20000425

AB A peptide consisting of an invariable 26-amino-acid-long region, named IR6, which is antigenically conserved among strains and species of the *B. burgdorferi* sensu lato complex, and immunodominant in both human and nonhuman primate hosts, is described. This peptide is characterized by the sequence MKKDDQIAAMVLRGMAKDGFALKD. This peptide is useful for rapid and specific diagnosis of Lyme disease, as are proteins contg. this peptide and nucleic acid sequences encoding this peptide and these proteins. Also provided is a novel ELISA, which is characterized by high sensitivity and specificity.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 42 CAPLUS COPYRIGHT 2002 ACS

AN 2001:374814 CAPLUS

DN 135:151479

TI Early induction of gamma interferon and interleukin-10 production in draining lymph nodes from mice infected with \*\*\**Borrelia*\*\*\* *burgdorferi*

AU Ganapamo, Frederic; Dennis, Vida A.; \*\*\*Philipp, Mario T.\*\*\*

CS Department of Parasitology, Tulane Regional Primate Research Center,  
Tulane University Health Sciences Center, Covington, LA, 70433, USA

SO Infect. Immun. (2000), 68(12), 7162-7165

CODEN: INFIBR; ISSN: 0019-9567

PB American Society for Microbiology

DT Journal

LA English

AB Lymph node (LN) cells from C3H/HeJ mice (Lyme disease susceptible) infected for 1 wk with \*\*\*Borrelia\*\*\* burgdorferi strain JD1 produced higher levels of gamma interferon (IFN-.gamma.) when stimulated in vitro with *B. burgdorferi* spirochetes than equiv. cells from B. burgdorferi-infected C57BL/6J mice (disease resistant). The interleukin-10 (IL-10) levels were comparable in the two strains, whereas the IL-4 levels were below detection limits. *B. burgdorferi*-stimulated LN cells from C57BL/6J mice produced significantly higher levels of IFN-.gamma. in the presence of neutralizing anti-IL-10 antibody than cells cultured with *B. burgdorferi* alone. No effect of IL-10 neutralization on IFN-.gamma. prodn. by LN cells from C3H/HeJ mice was obsd. Neutralizing antibody to IFN-.gamma. had no effect on the prodn. of IL-10 by LN cells from C57BL/6J mice. A slight decrease in IL-10 prodn. was detected in culture supernatants of equiv. cells from C3H/HeJ mice. The differential effect of IL-10 on IFN-.gamma. prodn. in C57BL/6J and C3H/HeJ mice suggests that IL-10 is probably involved in the regulation of IFN-.gamma. prodn. by LN cells during infection and may be at the root of the differential susceptibility to Lyme arthritis in these two strains of mice.

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 42 CAPLUS COPYRIGHT 2002 ACS

AN 2001:374745 CAPLUS

DN 135:136324

TI Interleukin-10 modulates proinflammatory cytokines in the human monocytic cell line THP-1 stimulated with \*\*\*Borrelia\*\*\* burgdorferi lipoproteins

AU Murthy, P. K.; Dennis, Vida A.; Lasater, Barbara L.; \*\*\*Philipp, Mario\*\*\*  
\*\*\* T.\*\*\*

CS Department of Parasitology, Tulane Regional Primate Research Center,  
Tulane University Health Sciences Center, Covington, LA, USA

SO Infect. Immun. (2000), 68(12), 6663-6669

CODEN: INFIBR; ISSN: 0019-9567

PB American Society for Microbiology

DT Journal

LA English

AB The authors detd. previously that lipoproteins of *B. burgdorferi* stimulate inflammatory and anti-inflammatory cytokines [interleukin-10 (IL-10)] in monocytes. IL-10 could have an effect on innate and acquired immune responses to *B. burgdorferi* and influence the magnitude of the infectious inoculum and disease outcome. To understand the mechanism(s) of IL-10 action during early infection, when innate immunity expressed chiefly by skin macrophages is key, the authors investigated the effect of exogenous and endogenous IL-10 on the prodn. of the macrophage-derived cytokines IL-6, IL-1.beta., IL-12, and tumor necrosis factor .alpha. (TNF-.alpha.). They used the THP-1 human monocytic cell line and recombinant lipidated OspA (L-OspA) as the model target cell and stimulant, resp. To det. the kinetics of cytokine prodn. by THP-1 cells, the authors stimulated them with L-OspA and also with heat-killed *B. burgdorferi* cells (HBB) and lipopolysaccharide (LPS). Exogenous IL-10 dampened prodn. of inflammatory

cytokines, as elicited by lipoproteins. The inhibition of endogenous IL-10 function by anti-IL-10 antibody reduced the prodn. of IL-12 and IL-6 but not that of IL-1.bet. and TNF-.alpha.. An inspection of the kinetics of cytokine prodn. clarified this finding. TNF-.alpha. was produced prior to, and IL-.beta. was produced at the same time as, IL-10, whereas IL-6 and IL-12 were produced later. HBb, LPS, and L-OspA yielded similar kinetics of cytokine prodn. Thus, lipoproteins are the functional mols. in HBb and perhaps in vivo. Also, signaling pathways utilized by LPS and lipoproteins may be extensively shared. The results are consistent with a major role played by IL-10 in controlling the initial phase of infection with this spirochete.

RE.CNT 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 14 OF 42 CAPLUS COPYRIGHT 2002 ACS

AN 2001:160687 CAPLUS

DN 135:271683

TI Characterization of a \*\*\*Borrelia\*\*\* burgdorferi VlsE invariable region useful in canine lyme disease serodiagnosis by enzyme-linked immunosorbent assay

AU Liang, Fang Ting; Jacobson, Richard H.; Straubinger, Reinhard K.; Grooters, Amy; \*\*\*Philipp, Mario T.\*\*\*

CS Department of Parasitology, Tulane Regional Primate Research Center, Tulane University Health Sciences Center, Covington, LA, 70433, USA

SO J. Clin. Microbiol. (2000), 38(11), 4160-4166

CODEN: JCMIDW; ISSN: 0095-1137

PB American Society for Microbiology

DT Journal

LA English

AB Sera collected from dogs exptl. infected with \*\*\*Borrelia\*\*\* burgdorferi by tick inoculation were analyzed for an antibody response to each of the six invariable regions (IRs; i.e., IR1 to IR6) of VlsE, the variable surface antigen of *B. burgdorferi*. Six synthetic peptides (C1 to C6), which reproduced the six IR sequences were used as peptide-based, ELISA antigens. Two IRs, IR2 and IR6, were found to be immunodominant. Studies with serially collected serum samples from exptl. infected dogs revealed that the antibody response to IR6 appears earlier and is stronger than that to IR2. Thus, the IR6 sequence alone appeared to be sufficient for serodiagnosis. When C6 alone was used as antigen, the peptide-based ELISA was pos. in 7 of 23 dogs (30%) as early as 3 wk postinfection. All dogs (n = 33) became strongly pos. 1 or 2 wk later, and this response persisted for the entire study, which lasted for 69 wk. Of 55 sera submitted by veterinarians from dogs suspected of having Lyme disease, 19 were also pos. by the C6 ELISA, compared to 20 positives detected by immunoblot anal. using cultured *B. burgdorferi* lysates as antigen. The sensitivity of using C2 and C6 together for detecting specific antibody in both exptl. infected and clin. diagnosed dogs was not better than sensitivity with C6 alone, confirming that C6 suffices as a diagnostic probe. Moreover, the C6 ELISA yielded 100% specificity with serum samples collected from 70 healthy dogs, 14 dogs with infections other than *B. burgdorferi*, and 15 animals vaccinated with either outer surface protein A, whole-spirochete vaccines, or the common puppy-vaccines. Therefore, this C6 ELISA was both sensitive and specific for the serodiagnosis of canine Lyme disease and could be used with vaccinated dogs.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 15 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

5

AN 2000:295696 BIOSIS

DN PREV200000295696

TI Cryptic and exposed invariable regions of VlsE, the variable surface antigen of \*\*\*Borrelia\*\*\* burgdorferi sl.

AU Liang, Fang Ting; Nowling, Jena M.; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Tulane Regional Primate Research Center, Tulane University Medical Center, 18703 Three Rivers Rd., Covington, LA, 70433 USA

SO Journal of Bacteriology, (June, 2000) Vol. 182, No. 12, pp. 3597-3601.  
print.

ISSN: 0021-9193.

DT Article

LA English

SL English

AB \*\*\*Borrelia\*\*\* burgdorferi, the Lyme disease spirochete, possesses a surface protein, VlsE, which undergoes antigenic variation. VlsE contains two invariable domains and a variable one that includes six variable and six invariable regions (IRs). Five of the IRs are conserved among strains and genospecies of *B. burgdorferi sensu lato*. IR6 is conserved, immunodominant, and exposed at the VlsE surface but not at the spirochete surface, as assessed in vitro. In the present study, the remaining conserved IRs (IR2 to IR5) were investigated. Antisera to synthetic peptides based on each of the IR2 to IR5 sequences were produced in rabbits. Antipeptide antibody titers were similarly high in all antisera. Native VlsE was immunoprecipitable with antibodies to IR2, IR4, and IR5 but not to IR3, indicating that the first three sequences were exposed at the VlsE surface. However, negative surface immunofluorescence and in vitro antibody-mediated killing results indicated that none of the IRs were accessible to antibody at the spirochetal surface in vitro.

L2 ANSWER 16 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

6

AN 2000:182068 BIOSIS

DN PREV200000182068

TI Epitope mapping of the immunodominant invariable region of \*\*\*Borrelia\*\*\* burgdorferi VlsE in three host species.

AU Liang, Fang Ting; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Tulane Regional Primate Research Center, Tulane University Medical Center, 18703 Three Rivers Rd., Covington, LA, 70433 USA

SO Infection and Immunity, (April, 2000) Vol. 68, No. 4, pp. 2349-2352.  
ISSN: 0019-9567.

DT Article

LA English

SL English

AB VlsE, the variable surface antigen of \*\*\*Borrelia\*\*\* burgdorferi, contains a 26-amino-acid-long immunodominant invariable region, IR6. In the present study, three overlapping 14-mer peptides reproducing the sequence of IR6 were used as peptide-based enzyme-linked immunosorbent assay antigens to map this invariable region in infected monkeys, mice, and human Lyme disease patients. Antibodies of the two primate species appeared to recognize IR6 as a single antigenic determinant, while mouse antibodies recognized multiple epitopes within this region.

L2 ANSWER 17 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

7

AN 2001:14279 BIOSIS

DN PREV200100014279

TI Antigenic conservation of an immunodominant invariable region of the VlsE  
lipoprotein among European pathogenic genospecies of \*\*\*Borrelia\*\*\*  
burgdorferi SL.

AU Liang, Fang Ting; Aberer, Elisabeth; Cinco, Marina; Gern, Lise; Hu, Chang  
Min; Lobet, Yves N.; Ruscio, Maurizio; Voet, Pierre E., Jr.; Weynants,  
Vincent E.; \*\*\*Philippe, Mario T. (1)\*\*\*

CS (1) Dept. of Parasitology, Tulane Regional Primate Research Center, Tulane  
University Medical Center, Covington, LA, 70433: philipp@tpc.tulane.edu  
USA

SO Journal of Infectious Diseases, (November, 2000) Vol. 182, No. 5, pp.  
1455-1462. print.  
ISSN: 0022-1899.

DT Article

LA English

SL English

AB Lyme disease is caused by genetically divergent spirochetes, including 3  
pathogenic genospecies: \*\*\*Borrelia\*\*\* burgdorferi sensu stricto, B.  
garinii, and B. afzelii. Serodiagnosis is complicated by this genetic  
diversity. A synthetic peptide (C6), based on the 26-mer invariable region  
(IR6) of the variable surface antigen of B. burgdorferi (VlsE), was used  
as ELISA antigen, to test serum samples collected from mice experimentally  
infected with the 3 genospecies and from European patients with Lyme  
disease. Regardless of the infecting strains, mice produced a strong  
antibody response to C6, which indicates that IR6 is antigenically  
conserved among the pathogenic genospecies. Twenty of 23 patients with  
culture-confirmed erythema migrans had a detectable antibody response to  
C6. A sensitivity of 95.2% was achieved, with serum samples collected from  
patients with well-defined acrodermatitis chronica atrophicans. Fourteen  
of 20 patients with symptoms of late Lyme disease also had a positive  
anti-IR6 ELISA. Thus, it is possible that C6 may be used to serodiagnose  
Lyme disease universally.

L2 ANSWER 18 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

8

AN 2000:88428 BIOSIS

DN PREV200000088428

TI DNA-binding proteins possibly involved in regulation of the  
post-logarithmic-phase expression of lipoprotein P35 in \*\*\*Borrelia\*\*\*  
burgdorferi.

AU Indest, Karl J.; \*\*\*Philippe, Mario T. (1)\*\*\*

CS (1) 18703 Three Rivers Rd., T. R. P. R. C., Covington, LA, 70433 USA

SO Journal of Bacteriology, (Jan., 2000) Vol. 182, No. 2, pp. 522-525.  
ISSN: 0021-9193.

DT Article

LA English

SL English

AB Previously, we have shown that the transcription of p35, a lipoprotein  
gene of \*\*\*Borrelia\*\*\* burgdorferi, is upregulated or initiated during  
the post-logarithmic bacterial growth phase in vitro. To identify  
potential regulatory factors, we examined the formation of DNA-protein

complexes by electromobility shift assay, using a 157-bp DNA fragment that spans the p35 promoter region and cell-free extracts of spirochetes harvested from both logarithmic and stationary growth phases. The binding properties of the extracts with the promoter region of the flaB gene, a constitutively expressed, growth-phase-independent gene, were also compared. The results from these experiments demonstrate that *B. burgdorferi* stationary-phase cell-free extracts have a growth-phase-dependent DNA binding protein that interacts specifically with the p35 promoter region. We show, in addition, that a segment from the 157-bp p35 promoter region which contains both a T-rich stretch and an inverted repeat is able to compete off the stationary-phase-specific complex when the segment is present in molar excess.

L2 ANSWER 19 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

9

AN 2002:140402 BIOSIS

DN PREV200200140402

TI Transcriptional regulation in spirochetes.

AU Indest, Karl J.; Ramamoorthy, Ramesh; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Department of Parasitology, Tulane Regional Primate Research Center, Tulane University Medical Center, 18703 Three Rivers Road, Covington, LA, 70433: philipp@tpc.tulane.edu USA

SO Journal of Molecular Microbiology and Biotechnology, (October, 2000) Vol. 2, No. 4, pp. 473-481. <http://www.jmmb.net>. print.

ISSN: 1464-1801.

DT General Review

LA English

AB Spirochetes belong to a widely diverse family of bacteria. Several species in this family can cause a variety of illnesses including syphilis and Lyme disease. Despite the fact that the complete genome sequence of two species, \*\*\**Borrelia*\*\*\* *burgdorferi* and *Treponema pallidum*, have been deciphered, much remains to be understood about spirochetal gene regulation. In this review we focus on the environmental transitions that spirochetes undergo during their life cycles and the mechanisms of transcriptional regulation that might possibly mediate spirochetal adaptations to such changes.

L2 ANSWER 20 OF 42 CAPLUS COPYRIGHT 2002 ACS

AN 1999:34932 CAPLUS

DN 130:109201

TI Surface antigens and proteins useful in compositions for the diagnosis and prevention of Lyme disease

IN \*\*\*Philipp, Mario T.\*\*\*

PA The Administrators of the Tulane Educational Fund, USA

SO PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 9900413 A1 19990107 WO 1998-US13551 19980629  
W: AU, BR, CA, CN, CZ, HU, ID, IL, JP, KR, MX, NO, NZ, PL, TR, US  
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE

AU 9881772 A1 19990119 AU 1998-81772 19980629  
EP 1012181 A1 20000628 EP 1998-931729 19980629  
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, FI  
ZA 9805704 A 19990113 ZA 1998-5704 19980630  
NO 9906514 A 20000214 NO 1999-6514 19991228  
PRAI US 1997-51271 P 19970630  
WO 1998-US13551 W 19980629

AB A novel isolated \*\*\*Borrelia\*\*\* burgdorferi sensu lato surface antigen is characterized by a relative mol. mass of 39.5 kDa. This antigen is expressed in vitro by spirochetes of a B. burgdorferi sensu lato strain. This antigen induces antibodies which kill spirochetes of a B. burgdorferi sensu lato strain by ADCK in vitro. Novel \*\*\*Borrelia\*\*\* cassette string protein or fragments thereof are also useful, as is the P39.5 protein in diagnosing Lyme disease and in compns. for treatment or prophylaxis thereof.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 21 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

10

AN 2000:63018 BIOSIS

DN PREV200000063018

TI Analysis of antibody response to invariable regions of VlsE, the variable surface antigen of \*\*\*Borrelia\*\*\* burgdorferi.

AU Liang, Fang Ting; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Tulane Regional Primate Research Center, Tulane University Medical Center, 18703 Three Rivers Rd., Covington, LA USA

SO Infection and Immunity, (Dec., 1999) Vol. 67, No. 12, pp. 6702-6706.  
ISSN: 0019-9567.

DT Article

LA English

SL English

AB VlsE, the variable surface antigen of \*\*\*Borrelia\*\*\* burgdorferi, consists of two invariable domains at the amino and carboxyl termini and one central variable domain. The latter contains six invariable regions, IR1 to IR6, and six variable regions. In the present study, the antigenicity of all of the invariable regions in B. burgdorferi-infected monkeys, humans, and mice was assessed by peptide-based enzyme-linked immunosorbent assays. Only one invariable region, IR6, was antigenic in all animals of the three host species. IR2 and IR4 were also antigenic in mice.

L2 ANSWER 22 OF 42 CAPLUS COPYRIGHT 2002 ACS

AN 1999:736895 CAPLUS

DN 132:48719

TI An immunodominant conserved region within the variable domain of VlsE, the variable surface antigen of \*\*\*Borrelia\*\*\* burgdorferi

AU Liang, Fang Ting; Alvarez, Alida L.; Gu, Yan; Nowling, Jena M.; Ramamoorthy, Ramesh; \*\*\*Philipp, Mario T.\*\*\*

CS Department of Parasitology, Tulane Regional Primate Research Center, Tulane University Medical Center, Covington, LA, 70433, USA

SO J. Immunol. (1999), 163(10), 5566-5573  
CODEN: JOIMA3; ISSN: 0022-1767

PB American Association of Immunologists

DT Journal

LA English

AB Antigenic variation is an effective strategy evolved by pathogenic microbes to avoid immune destruction. Variable Ags such as the variable major protein of \*\*\**Borrelia*\*\*\* hermsii, the variant surface glycoprotein of African trypanosomes, and the pilin of *Neisseria gonorrhoeae* include an immunodominant variable domain and one or more invariable domains that are not antigenic. Short, non-antigenic, invariable regions also may be present within the variable domain. VlsE (variable major protein-like sequence, expressed), the variable surface Ag of \*\*\**Borrelia*\*\*\* burgdorferi, the Lyme disease spirochete, also contains both variable and invariable domains. In addn., interspersed within the VlsE variable domain there are six invariable regions (IR1-6) that together amt. to half of this portion's primary structure. The authors show here that these IRs are conserved among strains and genospecies of the *B. burgdorferi* sensu lato complex. Surprisingly, unlike the invariable regions of variable major protein, variant surface glycoprotein, and pilin, which are not antigenic in natural infections, the most conserved of the IRs, IR6, is immunodominant in Lyme disease patients and in monkeys infected with *B. burgdorferi*. IR6 is exposed on the surface of VlsE, as assessed by immunopptn. expts., but is inaccessible to Ab on the spirochete's outer membrane, as demonstrated by immunofluorescence and in vitro killing assays. VlsE thus significantly departs from the antigenic variation paradigm, whereby immunodominance is only manifest in variable portions. The authors submit that IR6 may act as a decoy epitope(s) and contribute to divert the Ab response from other, perhaps protective regions of VlsE.

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 23 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1999:375432 BIOSIS

DN PREV199900375432

TI Positive IgG Western blot for \*\*\**Borrelia*\*\*\* burgdorferi in Colombia.

AU Palacios, Ricardo (1); Osorio, Lyda E.; Giraldo, Luis E.; Torres, Antonio J.; \*\*\*Philipp, Mario T.\*\*\* ; Ochoa, Maria Teresa

CS (1) Centro Internacional de Entrenamiento e Investigaciones Medicas (CIDEIM), Cali Colombia

SO Memorias do Instituto Oswaldo Cruz, (July-Aug., 1999) Vol. 94, No. 4, pp. 499-503.

ISSN: 0074-0276.

DT Article

LA English

SL English

AB In order to evaluate the presence of specific IgG antibodies to \*\*\**Borrelia*\*\*\* burgdorferi in patients with clinical manifestations associated with Lyme \*\*\*borreliosis\*\*\* in Cali, Colombia, 20 serum samples from patients with dermatologic signs, one cerebrospinal fluid (CSF) sample from a patient with chronic neurologic and arthritic manifestations, and twelve serum samples from individuals without clinical signs associated with Lyme \*\*\*borreliosis\*\*\* were analyzed by IgG Western blot. The results were interpreted following the recommendations of the Centers for Diseases Control and Prevention (CDC) for IgG Western blots. Four samples fulfilled the CDC criteria: two serum specimens from patients with morphea (localized scleroderma), the CSF from the patient with neurologic and arthritic manifestations, and one of the controls.

Interpretation of positive serology for Lyme disease in non-endemic countries must be cautious. However these results suggest that the putative "Lyme-like" disease may correlate with positivity on Western blots, thus raising the possibility that a spirochete genospecies distinct from *B. burgdorferi* sensu stricto, or a \*\*\**Borrelia*\*\*\* species other than *B. burgdorferi* sensu lato is the causative agent. Future work will focus on a survey of the local tick and rodent population for evidence of spirochete species that could be incriminated as the etiologic agent.

L2 ANSWER 24 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

11

AN 1999:259113 BIOSIS

DN PREV199900259113

TI Killing of \*\*\**Borrelia*\*\*\* *burgdorferi* by antibody elicited by OspA vaccine is inefficient in the absence of complement.

AU Nowling, Jena M.; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) TRPRC, 18703 Three Rivers Rd., Covington, LA, 70433 USA

SO Infection and Immunity, (Jan., 1999) Vol. 67, No. 1, pp. 443-445.

ISSN: 0019-9567.

DT Article

LA English

SL English

AB A Lyme disease vaccine, based on the \*\*\**Borrelia*\*\*\* *burgdorferi* lipoprotein OspA, has recently undergone phase III trials in humans. The results of one of these trials indicate that vaccine efficacy positively correlates with anti-OspA antibody titer. Spirochete killing within the tick vector midgut, upon which vaccine efficacy appears to depend, may occur chiefly via a mechanism that involves antibody alone, as it has been reported that complement is degraded by tick saliva decomplementing factors. We compared the in vitro killing efficiencies of anti-OspA antibody elicited in rhesus monkeys by the OspA vaccine, in the presence and in the absence of monkey complement. Killing in the absence of complement was between 14 and 3,800 times less efficient than with complement present, depending on the spirochete strain. The relative inefficiency of the complement-independent killing mechanism by anti-OspA antibody may explain why OspA vaccine efficacy is critically dependent on antibody titer.

L2 ANSWER 25 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

12

AN 1999:246843 BIOSIS

DN PREV199900246843

TI Induction of pro- and anti-inflammatory cytokines by \*\*\**Borrelia*\*\*\* *burgdorferi* lipoproteins in monocytes is mediated by CD14.

AU Giambartolomei, Guillermo H.; Dennis, Vida A. (1); Lasater, Barbara L.; \*\*\*Philipp, Mario T.\*\*\*

CS (1) Department of Parasitology, Tulane Regional Primate Research Center, 18703 Three Rivers Rd., Covington, LA, 70433 USA

SO Infection and Immunity, (Jan., 1999) Vol. 67, No. 1, pp. 140-147.

ISSN: 0019-9567.

DT Article

LA English

SL English

AB We previously showed that heat-killed \*\*\**Borrelia*\*\*\* *burgdorferi* spirochetes and lipidated outer surface protein A (L-OspA) stimulated the

in vitro production of interleukin-10 (IL-10) in peripheral blood mononuclear cells (PBMC) from uninfected humans and rhesus monkeys (G. Giambartolomei et al., Infect. Immun. 66:2691-2697, 1998). Here we demonstrate that uninfected human peripheral blood monocytes, but not B or T cells, are the cells that transcribe the IL-10 cytokine gene in response to heat-killed *B. burgdorferi*. *B. burgdorferi* similarly induced an upregulation of the IL-1beta and IL-6 cytokine genes in monocytes and the production of IL-10 and IL-6 in culture supernatants of the human monocytic cell line THP-1. Purified L-OspA (but not unlipidated OspA (U-OspA) or U-OspC) also stimulated the production of both cytokines in THP-1 cells in a dose-dependent fashion, suggesting that acylation of the OspA protein molecule is required for the production of both anti- and pro-inflammatory cytokines in naive monocytes. A lipohexapeptide that contained the tripalmitoyl-modified cysteine motif (Pam3Cys-Hex) of *B. burgdorferi* lipoproteins but with an arbitrary peptide sequence had the same effect. Monoclonal antibodies (MAbs) MY4 and 60bca, both of which bind to CD14 and are known to block lipopolysaccharide (LPS)-mediated cytokine production, were able to block L-OspA-mediated IL-10 and IL-6 cytokine production. In contrast, MAb 26ic, which also binds to CD14 but does not block LPS function, failed to inhibit L-OspA-mediated cytokine production. These data suggest that activation of monocytes and production of both anti- and pro-inflammatory cytokines induced by lipoproteins proceeds via the CD14 receptor. LPS binding protein was not required for OspA-induced cytokine production. Our results demonstrate that pro- and anti-inflammatory cytokines induced by *B. burgdorferi* lipoproteins in PBMC are produced by monocytes and that lipoprotein and LPS signaling pathways share at least the initial signaling event that involves the CD14 receptor.

L2 ANSWER 26 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

13

AN 1998:510276 BIOSIS

DN PREV199800510276

TI Differential expression of \*\*\*Borrelia\*\*\* *burgdorferi* proteins during growth in vitro.

AU Ramamoorthy, Ramesh; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) TRPRC, 18703 Three Rivers Road, Covington, LA 70433 USA

SO Infection and Immunity, (Nov., 1998) Vol. 66, No. 11, pp. 5119-5124.

ISSN: 0019-9567.

DT Article

LA English

AB In an earlier paper we described the transcriptionally regulated differential levels of expression of two lipoproteins of \*\*\*Borrelia\*\*\* *burgdorferi*, P35 and P7.5, during growth of the spirochetes in culture from logarithmic phase to stationary phase (K. J. Indest, R. Ramamoorthy, M. Sole, R. D. Gilmore, B. J. B. Johnson, and M.T. Philipp, Infect. Immun. 65: 1165-1171, 1997). Here we further assess this phenomenon by investigating whether the expression of other antigens of *B. burgdorferi*, including some well-characterized ones, are also regulated in a growth-phase-dependent manner in vitro. These studies revealed 13 additional antigens, including OspC, BmpD, and GroEL, that were upregulated 2- to 66-fold and a 28-kDa protein that was downregulated 2- to 10-fold, during the interval between the logarithmic- and stationary-growth phases. Unlike with these in vitro-regulated proteins, the levels of expression of OspA, OspB, P72, flagellin, and BmpA remained

unchanged throughout growth of the spirochetes in culture. Furthermore, ospAB, bmpAB, groEL, and fla all exhibited similar mRNA profiles, which is consistent with the constitutive expression of these genes. By contrast, the mRNA and protein profiles of ospC and bmpD indicated regulated expression of these genes. While bmpD exhibited a spike in mRNA expression in early stationary phase, ospC maintained a relatively higher level of mRNA throughout culture. These findings demonstrate that there are additional genes besides P7.5 and P35 whose regulated expression can be investigated in vitro and which may thus serve as models to facilitate the study of regulatory mechanisms in an organism that cycles between an arthropod and a vertebrate host.

L2 ANSWER 27 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

14

AN 1998:304921 BIOSIS

DN PREV199800304921

TI \*\*\**Borrelia*\*\*\* burgdorferi stimulates the production of interleukin-10 in peripheral blood mononuclear cells from uninfected humans and rhesus monkeys.

AU Giambartolomei, Guillermo H.; Dennis, Vida A. (1); \*\*\*Philipp, Mario\*\*\*  
\*\*\* T.\*\*\*

CS (1) Dep. Parasitol., Tulane Regional Primate Res. Center, 18703 Three Rivers Rd., Covington, LA 70433 USA

SO Infection and Immunity, (June, 1998) Vol. 66, No. 6, pp. 2691-2697.  
ISSN: 0019-9567.

DT Article

LA English

AB Heat-killed \*\*\**Borrelia*\*\*\* burgdorferi spirochetes stimulate in vitro production of interleukin-10 (IL-10) at both mRNA and protein levels in peripheral blood mononuclear cells (PBMC) of uninfected rhesus monkeys. A concomitant down-modulation of IL-2 gene transcription was observed. Neither IL-4 nor gamma interferon gene expression was ostensibly affected by *B. burgdorferi* spirochetes. These phenomena were observed regardless of whether the stimulating spirochetes belonged to the *B. burgdorferi* sensu stricto, \*\*\**Borrelia*\*\*\* afzelii, or \*\*\**Borrelia*\*\*\* garinii genospecies, the three main species that cause Lyme disease. *B. burgdorferi* also induced production of IL-10 in uninfected human PBMC, indicating that this effect might play a role in human Lyme disease. Purified lipidated outer surface protein A (OspA), but not its unlipidated form, induced the production of high levels of IL-10 in uninfected human PBMC. Thus, the lipid moiety is essential in the induction of IL-10 in these PBMC. *B. burgdorferi* M297, a mutant strain that lacks the plasmid that encodes OspA and OspB, also induced IL-10 gene transcription in PBMC, indicating that this phenomenon is not causally linked exclusively to OspA and its lipid moiety. These results demonstrate that *B. burgdorferi* can stimulate the production of an antiinflammatory, immunosuppressive cytokine in naive cells and suggest that IL-10 may play a role both in avoidance by the spirochete of deleterious immune responses and in limiting the inflammation that the spirochete is able to induce.

L2 ANSWER 28 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

15

AN 1998:304900 BIOSIS

DN PREV199800304900

TI \*\*\**Borrelia*\*\*\* burgdorferi escape mutants that survive in the presence

of antiserum to the OspA vaccine are killed when complement is also present.  
AU Sole, Monica; Bantar, Carlos; Indest, Karl; Gu, Yan; Ramamoorthy, Ramesh;  
Coughlin, Richard; \*\*\*Philipp, Mario T. (1)\*\*\*  
CS (1) TRPRC, 18703 Three Rivers Rd., Covington, LA 70433 USA  
SO Infection and Immunity, (June, 1998) Vol. 66, No. 6, pp. 2540-2546.  
ISSN: 0019-9567.

DT Article

LA English

AB As an initial attempt to investigate the possible role of outer surface protein A (OspA) escape mutants of \*\*\*Borrelia\*\*\* burgdorferi in decreasing the efficacy of the OspA vaccine, mutants of the HB19 strain of *B. burgdorferi* sensu stricto were selected in vitro from an uncloned, low-passage-number isolate. The antiserum used for selection was obtained from rhesus monkeys that had been given a vaccine of the same formulation and dose, and by the same route of administration, as that given to humans in several trials. All of the mutants selected in liquid medium and subsequently cloned twice in solid medium expressed a single abundant protein of 28 to 34 kDa instead of both OspA and OspB. Depending on the mutant, this protein reacted strongly, weakly, or not detectably with the anti-OspA antibody used for selection. Analysis of the ospAB locus of each of four representatives from these three groups of mutants by PCR with oligonucleotide primers that hybridize to flanking regions of the ospAB operon, and of the corresponding phenotype with monoclonal antibodies that bind to the amino or carboxyl terminus of the OspA or OspB polypeptide, indicated that in all cases a deletion within the operon had occurred. Spirochetes from the four mutant strains chosen for further analysis could be killed in antibody-dependent, complement-mediated killing assays with the selecting anti-OspA antibody, despite their resistance to killing with this antibody in the absence of complement. Complement-mediated killing occurred at an antibody concentration higher than that required to kill wild-type spirochetes. If anti-OspA antibody acts only within the tick, where complement is probably ineffective due to tick-derived decomplementing factors, then OspA escape mutants, if infectious, could seriously diminish the efficacy of OspA vaccines. On the other hand, if the killing of *B. burgdorferi* with anti-OspA antibody also takes place within the human host, then our results indicate that chimeric/deletion escape mutants will be killed as well.

L2 ANSWER 29 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1998:449818 BIOSIS

DN PREV199800449818

TI Pathogenesis of Lyme neuroborreliosis in the rhesus monkey: The early disseminated and chronic phases of disease in the peripheral nervous system.

AU Roberts, E. Donald (1); Bohm, Rudolf P., Jr.; Lowrie, Robert C., Jr.; Habicht, Gail; Katona, Laura; Piesman, Joseph; \*\*\*Philipp, Mario T.\*\*\*

CS (1) Tulane Regional Primate Res. Center, 18703 Three Rivers Rd., Covington, LA 70433 USA

SO Journal of Infectious Diseases, (Sept., 1998) Vol. 178, No. 3, pp. 722-732.

ISSN: 0022-1899.

DT Article

LA English

AB The histopathologic and immunohistochemical features of early and late

neuroborreliosis of the peripheral nervous system were investigated in rhesus macaques infected with the JD1 strain of \*\*\*Borrelia\*\*\* burgdorferi. Infection was proven by culture or polymerase chain reaction analysis of skin biopsies and indirectly by Western blot analysis. Three months after infection, neuritis involving multiple nerves was the most consistent neurologic manifestation. Both macrophages and B lymphocytes but not T lymphocytes were present in the cellular infiltrates. Axonal structures surrounding infiltrates had changes consisting of demyelination and axonal phagocytosis. Some of the Schwann cells in lesions stained with anti-nitrotyrosine and anti-tumor necrosis factor-alpha antibodies. B. burgdorferi, or antigens thereof, were visualized immunohistochemically within macrophages. Forty-six months after infection, the most common changes were regenerative, whereas neuritis was infrequent. Aberrant axonal regeneration, irregularly sized myelinated fibers, and fibrosis were frequently observed. Possible mechanisms to explain the appearance and subsidence of Lyme neuritis are discussed.

L2 ANSWER 30 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

16

AN 1998:48215 BIOSIS

DN PREV199800048215

TI The outer surface protein A (OspA) vaccine against Lyme disease: Efficacy in the rhesus monkey.

AU \*\*\*Philip, Mario T. (1)\*\*\* ; Lobet, Yves; Bohm, Rudolf P., Jr.; Roberts, E. Donald; Dennis, Vida A.; Gu, Yan; Lowrie,, Robert C., Jr.; Desmons, Pierre; Duray, Paul H.; England, John D.; Hauser, Pierre; Piesman, Joseph; Xu, Keyu

CS (1) Tulane Univ. Med. Cent., Tulane Regional Primate Res. Cent., Covington, LA USA

SO Vaccine, (Dec., 1997) Vol. 15, No. 17-18, pp. 1872-1887.

ISSN: 0264-410X.

DT Article

LA English

AB The efficacy of an outer surface protein A (OspA) vaccine in three different formulations was investigated in the rhesus monkey. The challenge infection was administered using Ixodes scapularis ticks that were infected with the B31 strain of \*\*\*Borrelia\*\*\* burgdorferi. Protection was assessed against both infection and disease, by a variety of procedures. Some of the animals were radically immune suppressed, as an attempt to reveal any putative low level infection in the vaccinated animals. The significant difference found between the spirochaetal infection rates of ticks that had fed on vaccinated vs. control monkeys, lack of seroconversion in the vaccinated animals, and the absence of spirochaetal DNA in the skin of vaccinated animals in the weeks following the challenge, indicate that vaccinated monkeys were protected against tick challenge. The postmortem immunohistochemical and polymerase chain reaction analyses, however, suggest that these monkeys may have undergone a low-level infection that was transient.

L2 ANSWER 31 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

17

AN 1997:203339 BIOSIS

DN PREV199799502542

TI Cell-density-dependent expression of \*\*\*Borrelia\*\*\* burgdorferi lipoproteins in vitro.

AU Indest, Karl J.; Ramamoorthy, Ramesh; Sole, Monica; Gilmore, Robert D.;

Johnson, Barbara J. B.; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) T.R.P.R.C., 18703 Three Rivers Rd., Covington, LA 70433 USA

SO Infection and Immunity, (1997) Vol. 65, No. 4, pp. 1165-1171.

ISSN: 0019-9567.

DT Article

LA English

AB Previously, we had identified non-OspA-OspB surface proteins of \*\*\*Borrelia\*\*\* burgdorferi that are targeted by the antibody-dependent complement-mediated killing mechanism. Here we demonstrate by Western blotting that one of these proteins, P35, is upregulated at the onset of stationary phase in vitro. Northern analysis revealed that the upregulation of P35 is at the level of transcription. In addition, the expression of an open reading frame (ORF) located downstream of the p35 gene was found to be regulated in the same fashion as that of P35. This ORF encodes a 7.5-kDa lipoprotein. The transcriptional start sites for both of these genes were determined, to aid in the identification of the putative promoter regions. Additional sequencing of the 5' flanking region of the p35 gene revealed a region of dyad symmetry 52 bp upstream of the transcription start site. Southern analysis demonstrated that the expression of these genes was not due to a cell-density-dependent rearrangement in the genome of *B. burgdorferi*. These findings provide an in vitro model for studying mechanisms of gene regulation in *B. burgdorferi*.

L2 ANSWER 32 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1997:169125 BIOSIS

DN PREV199799475728

TI Mononeuropathy multiplex in rhesus monkeys with chronic Lyme disease.

AU England, John D. (1); Bohm, Rudolf P., Jr.; Roberts, E. Donald;

\*\*\*Philipp, Mario T.\*\*\*

CS (1) Dep. Neurol., Louisiana State Univ. Sch. Med., 1542 Tulane Ave., New Orleans, LA 70112 USA

SO Annals of Neurology, (1997) Vol. 41, No. 3, pp. 375-384.

ISSN: 0364-5134.

DT Article

LA English

AB Peripheral neuropathy is a recognized but poorly understood manifestation of Lyme disease. We performed serial electrophysiological studies on 8 rhesus monkeys chronically infected with the JD1 strain of \*\*\*Borrelia\*\*\* burgdorferi and compared the results with those of similar studies on 10 uninfected control monkeys. Four infected and 2 uninfected animals underwent sural nerve biopsy. Five of the infected and 1 of the uninfected animals also had postmortem neuropathological examinations. Altogether, 5 of the infected monkeys demonstrated primarily axonal-loss-variety multifocal neuropathies. Only one nerve lesion exhibited findings compatible with demyelination. Pathologically, peripheral nerve specimens showed multifocal axonal degeneration and regeneration and occasional perivascular inflammatory cellular infiltrates without vessel wall necrosis. Free spirochetal structures were not seen, but several macrophages exhibited positive immunostaining with a highly specific anti-*B. burgdorferi*, 7.5-kd lipoprotein monoclonal antibody. In the infected animals, serial analysis of serum antibodies to *B. burgdorferi* showed increasing numbers of IgG specificities and new IgM specificities, suggesting persistent infection. Thus, peripheral

neuropathy in the form of a mononeuropathy multiplex develops frequently in rhesus monkeys chronically infected with *B. burgdorferi*. The pathogenesis of these nerve lesions is not yet known, but our studies suggest an immune-mediated process perhaps driven by persistent infection with *B. burgdorferi*.

L2 ANSWER 33 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1997:275052 BIOSIS

DN PREV199799574255

TI Lyme neuroborreliosis in the rhesus monkey.

AU England, John D. (1); Bohm., Rudolf P., Jr.; Roberts, E. Donald;

\*\*\*Philip, Mario T.\*\*\*

CS (1) Dep. Neurol., La. State Univ. Med. Cent., 1542 Tulane Ave., New Orleans, LA 70112 USA

SO Seminars in Neurology, (1997) Vol. 17, No. 1, pp. 53-56.

ISSN: 0271-8235.

DT General Review

LA English

L2 ANSWER 34 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

18

AN 1996:219217 BIOSIS

DN PREV199698775346

TI Molecular characterization, genomic arrangement, and expression of bmpD, a new member of the bmp class of genes encoding membrane proteins of \*\*\**Borrelia*\*\*\* *burgdorferi*.

AU Ramamoorthy, Ramesh; Povinelli, Laura; \*\*\*Philip, Mario T. (1)\*\*\*

CS (1) TRPRC, 18703 Three Rivers Rd., Covington, LA 70433 USA

SO Infection and Immunity, (1996) Vol. 64, No. 4, pp. 1259-1264.

ISSN: 0019-9567.

DT Article

LA English

AB An expression library made with \*\*\**Borrelia*\*\*\* *burgdorferi* DNA in the vector lambda-ZapII was screened with serum from a monkey infected with the Lyme disease agent. This serum killed *B. burgdorferi* in vitro by an antibody-dependent, complement-mediated mechanism and contained antibodies to at least seven spirochetal antigens, none of which were the major outer surface proteins OspA or OspB. Among several positive clones, a clone containing the *B. burgdorferi* bmpA gene encoding the immunodominant antigen P39 was obtained. Chromosome walking and DNA sequence analysis permitted the identification of two additional upstream genes homologous to the bmpA gene and its related companion, bmpB. The first of these was the recently characterized bmpC gene, and adjacent to it was the fourth and new member of this class, which has been designated bmpD. The gene product encoded by bmpD is 341 residues long, contains a signal sequence with a potential signal peptidase II cleavage site, and has 26% identity with TmpC of *Treponema pallidum*. Southern blotting confirmed the tandem arrangement of all four bmp genes in the chromosome of *B. burgdorferi* JD1. However, Northern (RNA) blotting revealed that bmpD is expressed as a monocistronic transcript, which indicates that it is not part of an operon at the bmp locus. The bmpD gene was found to be conserved in representative members of the three species of the *B. burgdorferi* sensu lato complex, suggesting that it serves an important biological function in the spirochete.

L2 ANSWER 35 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

19

AN 1996:221294 BIOSIS

DN PREV199698777423

TI Host DNA can interfere with detection of \*\*\*Borrelia\*\*\* burgdorferi in skin biopsy specimens by PCR.

AU Cogswell, Frank B.; Bantar, Carlos E.; Hughes, Theresa G.; Gu, Yan; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Tulane Primate Res. Cent., 18703 Three Rivers Rd., Covington, LA 70433 USA

SO Journal of Clinical Microbiology, (1996) Vol. 34, No. 4, pp. 980-982.  
ISSN: 0095-1137.

DT Article

LA English

AB It is demonstrated that a diagnostic PCR for \*\*\*Borrelia\*\*\* burgdorferi can be inhibited in the presence of more than 500 ng of host (monkey skin) DNA. The inhibitor is the host DNA itself. An acceptable value for analytical sensitivity can be obtained by diluting the skin-B. burgdorferi proteinase K lysate to a level below the inhibitory concentration of the host DNA. Dilution of the lysate may obviate the need for further DNA purification.

L2 ANSWER 36 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1996:348367 BIOSIS

DN PREV199699070723

TI Mononeuropathy multiplex in rhesus monkeys with chronic Lyme disease.

AU England, John D. (1); Bohm, Rudolf P.; Roberts, E. Donald; \*\*\*Philipp,\*\*\* \*\*\* Mario T.\*\*\*

CS (1) New Orleans, LA USA

SO Neurology, (1996) Vol. 46, No. 2 SUPPL., pp. A396.

Meeting Info.: 48th Annual Meeting of the American Academy of Neurology  
San Francisco, California, USA March 23-30, 1996  
ISSN: 0028-3878.

DT Conference

LA English

L2 ANSWER 37 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

20

AN 1996:529556 BIOSIS

DN PREV199699251912

TI \*\*\*Borrelia\*\*\* burgdorferi possesses a collagenolytic activity.

AU Grab, Dennis J. (1); Kennedy, Richard; \*\*\*Philipp, Mario T.\*\*\*

CS (1) Dep. Parasitol., Tulane Regional Primate Res. Cent., Covington, LA USA

SO FEMS Microbiology Letters, (1996) Vol. 144, No. 1, pp. 39-45.

ISSN: 0378-1097.

DT Article

LA English

AB Lyme disease is a multisystemic disorder caused by \*\*\*Borrelia\*\*\* burgdorferi, an invasive spirochete. B. burgdorferi has a predilection for collagenous tissue and one major clinical manifestation of the disease is arthritis. We have identified a collagenolytic activity in B. burgdorferi detergent lysates using iodinated gelatin as well as iodinated pepsinized human collagen types II and IV as protein substrates. In addition, we describe several proteolytic activities in B. burgdorferi with molecular masses greater than 200 kDa on sodium dodecyl sulfate polyacrylamide gels

containing copolymerized gelatin. We propose that the collagenolytic activity of *B. burgdorferi* has a role in invasion, in the pathogenesis of Lyme arthritis, and perhaps also in other manifestations of Lyme  
\*\*\*borreliosis\*\*\*.

L2 ANSWER 38 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1995:290767 BIOSIS

DN PREV199598305067

TI A family of homologous genes that includes the immunodominant antigen P39 in \*\*\**Borrelia*\*\*\* *burgdorferi*, the Lyme disease agent.

AU Ramamoorthy, Ramesh; Povinelli, Laura; \*\*\*Philipp, Mario T.\*\*\*

CS Tulane Primate Cent., Tulane Univ. Med. Cent., Covington, LA USA

SO Abstracts of the General Meeting of the American Society for Microbiology, (1995) Vol. 95, No. 0, pp. 253.

Meeting Info.: 95th General Meeting of the American Society for Microbiology Washington, D.C., USA May 21-25, 1995

ISSN: 1060-2011.

DT Conference

LA English

L2 ANSWER 39 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1995:173642 BIOSIS

DN PREV199598187942

TI Chronic Lyme disease in the Rhesus Monkey.

AU Roberts, E. Donald (1); Bohm, Rudolf P., Jr.; Cogswell, Frank B.; Lanners, H. Norbert; Lowrie, Robert C., Jr.; Povinelli, Laura; Piesman, Joseph; \*\*\*Philipp, Mario T.\*\*\*

CS (1) Tulane Regional Primate Res. Cent., 18703 Three Rivers Road, Covington, LA 70433 USA

SO Laboratory Investigation, (1995) Vol. 72, No. 2, pp. 146-160.

ISSN: 0023-6837.

DT Article

LA English

AB BACKGROUND: We have previously reported the clinical, pathologic, and immunologic features of "early" \*\*\**Borrelia*\*\*\* *burgdorferi* infection in rhesus monkeys (3). We have now evaluated these features during the chronic phase of Lyme disease in this animal model. EXPERIMENTAL DESIGN: Clinical signs, and pathologic changes at the gross and microscopic levels, were investigated 6 months post-infection in several organ systems of five rhesus macaques (*Macaca mulatta*), which were infected with \*\*\**Borrelia*\*\*\* *burgdorferi* by allowing infected *Ixodes scapularis* nymphal ticks to feed on them. A sixth animal was used as an uninfected control. \*\*\**Borrelia*\*\*\* antigens recognized by serum antibody were identified longitudinally by Western blot analysis, and C1q-binding immune complexes were quantified. Localization of the spirochete in the tissues was achieved by immunohistochemistry and in vitro culture. The species of spirocheta cultured was confirmed by the polymerase chain reaction.

RESULTS: Chronic arthritis was observed in five out of five animals. The knee and elbow joints were the most consistently affected. Articular cartilage necrosis and/or degenerative arthropathy were the most severe joint structural changes. Synovial cell hyperplasia and a mononuclear/lymphocyte infiltrate were commonly seen. Nerve lesions were also observed, including nerve sheath fibrosis and focal demyelination of the spinal cord. Peripheral neuropathy was observed in five out of five animals and could be correlated in the most severely affected monkey with

the presence of higher levels of circulating immune complexes. Differences in disease severity did not correlate with differences in the antigens recognized on Western blot analysis. CONCLUSIONS: *B. burgdorferi* infection in rhesus macaques mirrors several aspects of both the early and chronic phases of the disease in humans. This animal model will facilitate the study of the pathogenesis of Lyme arthritis and neuroborreliosis.

L2 ANSWER 40 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

21

AN 1994:547350 BIOSIS

DN PREV199598006898

TI \*\*\**Borrelia*\*\*\* *burgdorferi* Antigens That Are Targeted by Antibody-Dependent, Complement-Mediated Killing in the Rhesus Monkey.

AU Aydintug, M. Kemal; Gu, Yan; \*\*\*Philipp, Mario T. (1)\*\*\*

CS (1) Dep. Parasitol., Tulane Regional Primate Res. Cent., Tulane Univ. Med. Cent., Covington, LA 70433 USA

SO Infection and Immunity, (1994) Vol. 62, No. 11, pp. 4929-4937.

ISSN: 0019-9567.

DT Article

LA English

AB We identified surface antigens of \*\*\**Borrelia*\*\*\* *burgdorferi* that are targeted by antibody-dependent, complement-mediated killing (ADCK) in the rhesus monkey. For this purpose, we had available serum samples from three animals infected with *B. burgdorferi* JD1 by needle inoculation and from two monkeys that were infected with the same *B. burgdorferi* strain by *Ixodes scapularis* tick bite. Sera from monkeys from the first group contained antibodies to OspA and OspB detectable by Western blot (immunoblot) using whole *B. burgdorferi* antigens, whereas serum samples from animals in the second group did not. The targeting of OspA and OspB by functional antibodies was demonstrated directly by showing that ADCK was partially inhibited when antibodies were preincubated with an excess of soluble recombinant OspA or OspB. Simultaneous addition of OspA and OspB did not result in an additive inhibitory effect on ADCK, a result that suggests that the epitopes on OspA and that on OspB targeted by antibody in this mechanism are the same, or at least cross-reacting. The targeting of non-OspA, non-OspB surface antigens was inferred from the fact that sera from tick-inoculated animals, which did not contain detectable anti-OspA or anti-OspB antibodies, were able to effect ADCK. This killing effect was not inhibitable by the addition of recombinant OspA or OspB or both proteins together. We also showed that both immunoglobulin G and M antibodies participate in the ADCK mechanism in the rhesus monkey. Rhesus complement does not kill *B. burgdorferi* in vitro in the absence of antibody, and antibody alone is effective in killing only at serum dilutions lower than 1:15. However, such "complementindependent" antibodies were not present in all bleeds. Two main conclusions may be drawn from the analysis of our results. First, both OspA and OspB are targeted by the ADCK mechanism in the rhesus monkey. Second, one or more *B. burgdorferi* surface antigens that are neither OspA nor OspB also participate in ADCK.

L2 ANSWER 41 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1995:79737 BIOSIS

DN PREV199598094037

TI Animal models of Lyme disease: Pathogenesis and immunoprophylaxis.

AU \*\*\*Philipp, Mario T. (1)\*\*\* ; Johnson, Barbara J. B.

CS (1) Tulane Univ. Med. Cent., Tulane Regional Primate Res. Cent., 18703

Three Rivers Rd., Covington, LA 70433 USA

SO Trends in Microbiology, (1994) Vol. 2, No. 11, pp. 431-437.

ISSN: 0966-842X.

DT General Review

LA English

L2 ANSWER 42 OF 42 CAPLUS COPYRIGHT 2002 ACS

AN 1993:515080 CAPLUS

DN 119:115080

TI Early and early disseminated phases of Lyme disease in the rhesus monkey:

A model for infection in humans

AU \*\*\*Philipp, Mario T.\*\*\* ; Aydintug, M. Kemal; Bohm, Rudolf P., Jr.; Cogswell, Frank B.; Dennis, Vida A.; Lanners, H. Norbert; Lowrie, Robert C., Jr.; Roberts, E. Donald; Conway, Mandi D.; et al.

CS Med. Cent., Tulane Univ., Covington, LA, 70433, USA

SO Infect. Immun. (1993), 61(7), 3047-59

CODEN: INFIBR; ISSN: 0019-9567

DT Journal

LA English

AB The authors demonstrate that \*\*\*Borrelia\*\*\* burgdorferi infection in the rhesus monkey mimics the early and early disseminated phases of human Lyme disease. Clin., bacteriol., immunol., and pathol. signs of infection were investigated during 13 wk after inoculation of the spirochete. Three animals were given *B. burgdorferi* (strain JD1) by needle inoculations, six animals were exposed to the bite of *B. burgdorferi*-infected *Ixodes dammini* ticks, and three animals were uninfected controls. *B. burgdorferi* could be recovered from all animals that were given the spirochete. Bacteria were detectable until week 6 post-inoculation (p.i.) in blood, until week 8 p.i. in skin biopsies, and at 10 wk p.i. in the conjunctiva of one of two animals which developed conjunctivitis. Erythema migrans (EM) appeared in one of the three animals infected by needle inoculation and in five of the six animals infected by ticks. Deep dermal perivascular lymphocytic infiltrations (characteristic of human EM) were obsd. in all animals showing EM clin. Both EM and conjunctivitis were documented concomitantly with the presence of the spirochete. Lethargy, splenomegaly, and cerebrospinal fluid pleocytosis were also noted in some animals, but the direct connection of these signs with the infection was not shown. The appearance rate of IgM and IgG antibodies to *B. burgdorferi*, as well as the antigen spectra recognized, were remarkably similar to those seen in humans. Serum antibodies from infected animals were able to kill *B. burgdorferi* in vitro in the presence of rhesus complement. The rhesus monkey model appears to be useful for the investigation of the immunol. and pathogenesis of Lyme disease and for the development of immunoprophylactic, diagnostic, and chemotherapeutic protocols.

=> s borrel?

L3 34992 BORREL?

=> s l3 and p39.5

L4 1 L3 AND P39.5

=> d bib ab

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

AN 1999:34932 CAPLUS

DN 130:109201

TI Surface antigens and proteins useful in compositions for the diagnosis and prevention of Lyme disease

IN Philipp, Mario T.

PA The Administrators of the Tulane Educational Fund, USA

SO PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9900413	A1	19990107	WO 1998-US13551	19980629
W: AU, BR, CA, CN, CZ, HU, ID, IL, JP, KR, MX, NO, NZ, PL, TR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,				
PT, SE				
AU 9881772	A1	19990119	AU 1998-81772	19980629
EP 1012181	A1	20000628	EP 1998-931729	19980629
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, FI				
ZA 9805704	A	19990113	ZA 1998-5704	19980630
NO 9906514	A	20000214	NO 1999-6514	19991228

PRAI US 1997-51271 P 19970630

WO 1998-US13551 W 19980629

AB A novel isolated \*\*\*Borrelia\*\*\* burgdorferi sensu lato surface antigen is characterized by a relative mol. mass of 39.5 kDa. This antigen is expressed in vitro by spirochetes of a B. burgdorferi sensu lato strain. This antigen induces antibodies which kill spirochetes of a B. burgdorferi sensu lato strain by ADCK in vitro. Novel \*\*\*Borrelia\*\*\* cassette string protein or fragments thereof are also useful, as is the \*\*\*P39\*\*\* . \*\*\*5\*\*\* protein in diagnosing Lyme disease and in compns. for treatment or prophylaxis thereof.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l3 and ((39.5 kda)or(39.5 kilodalton?)or(39,500 dalton?))

L5 1 L3 AND ((39.5 KDA) OR(39.5 KILODALTON?) OR(39,500 DALTON?))

=> d bib ab

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

AN 1999:34932 CAPLUS

DN 130:109201

TI Surface antigens and proteins useful in compositions for the diagnosis and prevention of Lyme disease

IN Philipp, Mario T.

PA The Administrators of the Tulane Educational Fund, USA

SO PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9900413	A1	19990107	WO 1998-US13551	19980629
W: AU, BR, CA, CN, CZ, HU, ID, IL, JP, KR, MX, NO, NZ, PL, TR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,				
PT, SE				
AU 9881772	A1	19990119	AU 1998-81772	19980629
EP 1012181	A1	20000628	EP 1998-931729	19980629
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, FI				
ZA 9805704	A	19990113	ZA 1998-5704	19980630
NO 9906514	A	20000214	NO 1999-6514	19991228

PRAI US 1997-51271 P 19970630

WO 1998-US13551 W 19980629

AB A novel isolated \*\*\*Borrelia\*\*\* burgdorferi sensu lato surface antigen is characterized by a relative mol. mass of \*\*\*39\*\*\* . \*\*\*5\*\*\* \*\*\*kDa\*\*\* . This antigen is expressed in vitro by spirochetes of a B. burgdorferi sensu lato strain. This antigen induces antibodies which kill spirochetes of a B. burgdorferi sensu lato strain by ADCK in vitro. Novel \*\*\*Borrelia\*\*\* cassette string protein or fragments thereof are also useful, as is the P39.5 protein in diagnosing Lyme disease and in compns. for treatment or prophylaxis thereof.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l3 and vaccine? and (surface antigen?)

5 FILES SEARCHED...

L6 147 L3 AND VACCINE? AND (SURFACE ANTIGEN?)

=> dup rem l6

PROCESSING COMPLETED FOR L6

L7 123 DUP REM L6 (24 DUPLICATES REMOVED)

=> s l7 and vaccine?/ti and (surface antigen?)/ti

L8 0 L7 AND VACCINE?/TI AND (SURFACE ANTIGEN?)/TI

=> s l3 and ((p1-1)or(p3-1)or(p6-1)or(P9-1)or(P12-1))

4 FILES SEARCHED...

7 FILES SEARCHED...

L9 4 L3 AND ((P1-1) OR(P3-1) OR(P6-1) OR(P9-1) OR(P12-1))

=> dup rem l9

PROCESSING COMPLETED FOR L9

L10 2 DUP REM L9 (2 DUPLICATES REMOVED)

=> d bib ab 1-

YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L10 ANSWER 1 OF 2 CABA COPYRIGHT 2002 CABINET DUPLICATE 1

AN 93:141313 CABA

DN 930518616

TI Transmission risk of Lyme disease and implications for tick management

AU Ginsberg, H. S.

CS National Park Service Coastal Research Center, University of Rhode Island,

Woodward Hall-Plant Sciences/Entomology, Kingston, RI 02881, USA.  
SO American Journal of Epidemiology, (1993) Vol. 138, No. 1, pp. 65-73. 33  
ref.  
ISSN: 0002-9262

DT Journal

LA English

AB The transmission risk of Lyme disease at a site can be estimated using the probability of exposure ( $P_1$  = probability of being bitten by at least 1 infected tick);  $***P_1*** = ***1*** - (1 - k_t)n$ , where  $n$  = number of tick bites per person and  $k_t$  =  $***Borrelia***$  burgdorferi spirochaete prevalence in questing ticks (e.g. *Ixodes dammini* [i.e. "northern population" of *I. scapularis*]). This probability is more directly related to the likelihood of acquiring Lyme disease than the standard measure of transmission risk (the number of infected ticks per sample) and allows for direct consideration of the level of tick/human contact (by varying  $n$ ) in assessing exposure risk and designing management strategies. Projections predict that interventions that lower tick abundance or spirochaete prevalence do not necessarily result in equivalent declines in human exposure risk. Management interventions are predicted to have greatest success at lowering disease incidence in humans when tick abundance and/or pathogen prevalence in questing ticks are initially low (e.g. for ticks in residential lawns or for low-prevalence diseases). These techniques are predicted to be less effective at lowering disease incidence in people engaged in high-risk activities at sites with high tick abundance and pathogen prevalence, such as wooded sites in highly endemic areas.

L10 ANSWER 2 OF 2 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 93226350 EMBASE

DN 1993226350

TI Transmission risk of Lyme disease and implications for tick management.

AU Ginsberg H.S.

CS Vector-borne Disease Research Group, Natl. Park Svc. Coastal Res. Center,  
University of Rhode Island, Kingston, RI 02881, United States

SO American Journal of Epidemiology, (1993) 138/1 (65).

ISSN: 0002-9262 CODEN: AJEPAS

CY United States

DT Journal; General Review

FS 004 Microbiology

017 Public Health, Social Medicine and Epidemiology

LA English

SL English

AB Transmission risk of Lyme disease at a site can be estimated using the probability of exposure ( $P_1$  = probability of being bitten by at least one infected tick);  $***P_1*** = ***1*** - (1 - k(t))(n)$ , where  $n$  = number of tick bites per person and  $k(t)$  = spirochete prevalence in questing ticks. This probability is more directly related to the likelihood of acquiring Lyme disease than the standard measure of transmission risk (the number of infected ticks per sample) and allows for direct consideration of the level of tick/human contact (by varying  $n$ ) in assessing exposure risk and designing management strategies. Projections predict that interventions that lower tick abundance or spirochete prevalence do not necessarily result in equivalent declines in human exposure risk. Management interventions are predicted to have greatest success at lowering disease incidence in humans when tick abundance and/or

pathogen prevalence in questing ticks are initially low (e.g., for ticks in residential lawns or for low-prevalence diseases). These techniques are predicted to be less effective at lowering disease incidence in people engaged in high-risk activities at sites with high tick abundance and pathogen prevalence, such as wooded sites in highly endemic areas.

=> d bib ab 17 1-

YOU HAVE REQUESTED DATA FROM 123 ANSWERS - CONTINUE? Y/(N):y

L7 ANSWER 1 OF 123 USPATFULL

AN 2002:43671 USPATFULL

TI 49 human secreted proteins

IN Moore, Paul A., Germantown, MD, UNITED STATES

Ruben, Steven M., Olney, MD, UNITED STATES

Olsen, Henrik S., Gaithersburg, MD, UNITED STATES

Shi, Yanggu, Gaithersburg, MD, UNITED STATES

Rosen, Craig A., Laytonsville, MD, UNITED STATES

Florence, Kimberly A., Rockville, MD, UNITED STATES

Soppet, Daniel R., Centreville, VA, UNITED STATES

LaFleur, David W., Washington, DC, UNITED STATES

Endress, Gregory A., Potomac, MD, UNITED STATES

Ebner, Reinhard, Gaithersburg, MD, UNITED STATES

Komatsoulis, George, Silver Spring, MD, UNITED STATES

Duan, Roxanne D., Bethesda, MD, UNITED STATES

PI US 2002026040 A1 20020228

AI US 2001-904615 A1 20010716 (9)

RLI Continuation of Ser. No. US 2000-739254, filed on 19 Dec 2000, PENDING

Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED

Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999,

UNKNOWN

PRAI US 1998-97917 19980825 (60)

US 1998-98634 19980831 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 23

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 19401

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

L7 ANSWER 2 OF 123 USPATFULL

AN 2002:43187 USPATFULL

TI Transforming growth factor alpha HIII

IN Wei, Ying-Fei, Berkeley, CA, UNITED STATES

PI US 2002025553 A1 20020228

AI US 2000-726348 A1 20001201 (9)

RLI Continuation-in-part of Ser. No. US 1997-778545, filed on 3 Jan 1997,

PENDING

PRAI US 1996-11136 19960104 (60)  
US 1999-168387 19991202 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 25

ECL Exemplary Claim: 1

DRWN 5 Drawing Page(s)

LN.CNT 11810

AB The present invention relates to a novel human protein called Transforming Growth Factor Alpha III, and isolated polynucleotides encoding this protein. Also provided are vectors, host cells, antibodies, and recombinant methods for producing this human protein. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to this novel human protein.

L7 ANSWER 3 OF 123 USPATFULL

AN 2002:32536 USPATFULL

TI Compositions and methods for in vivo delivery of polynucleotide-based therapeutics

IN Manthorpe, Marston, San Diego, CA, UNITED STATES

Hartikka, Jukka, San Diego, CA, UNITED STATES

Sukhu, Loretta, San Diego, CA, UNITED STATES

PA Vical Incorporated, San Diego, CA (U.S. corporation)

PI US 2002019358 A1 20020214

AI US 2001-839574 A1 20010423 (9)

PRAI US 2000-198823 20000421 (60)

US 2000-253153 20001128 (60)

DT Utility

FS APPLICATION

LREP STERNE, KESSLER, GOLDSTEIN & FOX PLLC, 1100 NEW YORK AVENUE, N.W., SUITE 600, WASHINGTON, DC, 20005-3934

CLMN Number of Claims: 163

ECL Exemplary Claim: 1

DRWN 29 Drawing Page(s)

LN.CNT 4605

AB The present invention relates to pharmaceutical compositions and methods to improve expression of exogenous polypeptides into vertebrate cells in vivo, utilizing delivery of polynucleotides encoding such polypeptides. More particularly, the present invention provides the use of salts, in particular sodium and potassium salts of phosphate, in aqueous solution, and auxiliary agents, in particular detergents and surfactants, in pharmaceutical compositions and methods useful for direct polynucleotide-based polypeptide delivery into the cells of vertebrates.

L7 ANSWER 4 OF 123 USPATFULL

AN 2002:22131 USPATFULL

TI 18 Human secreted proteins

IN Shi, Yanggu, Gaithersburg, MD, UNITED STATES

Young, Paul E., Gaithersburg, MD, UNITED STATES

Ebner, Reinhard, Gaithersburg, MD, UNITED STATES

Soppet, Daniel R., Centreville, VA, UNITED STATES

Ruben, Steven M., Olney, MD, UNITED STATES

PI US 2002012966 A1 20020131  
AI US 2001-768826 A1 20010125 (9)  
RLI Continuation-in-part of Ser. No. WO 2000-US22350, filed on 15 Aug 2000,  
UNKNOWN  
PRAI US 1999-148759 19990816 (60)  
DT Utility  
FS APPLICATION  
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850  
CLMN Number of Claims: 23  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 18157  
AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

L7 ANSWER 5 OF 123 USPATFULL  
AN 2002:34422 USPATFULL  
TI Methods of inducing mucosal immunity  
IN Weiner, David B., Merion, PA, United States  
Wang, Bin, Havertown, PA, United States  
Ugen, Kenneth E., Philadelphia, PA, United States  
PA The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)  
PI US 6348449 B1 20020219  
AI US 1994-357398 19941216 (8)  
RLI Continuation-in-part of Ser. No. US 1993-125012, filed on 21 Sep 1993,  
now patented, Pat. No. US 5593972, issued on 14 Jan 1996

DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Crouch, Deborah  
LREP Woodcock Washburn, LLP  
CLMN Number of Claims: 9  
ECL Exemplary Claim: 1  
DRWN 8 Drawing Figure(s); 2 Drawing Page(s)  
LN.CNT 2479

CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Methods of inducing mucosal immunity in individuals against proteins and peptides are disclosed. The methods comprise the step of administering topically or by lavage into mucosal tissue selected from the group consisting of rectal, vaginal, urethral, sublingual and buccal, a nucleic acid molecule that comprises a nucleotide sequence that encodes a protein or peptide that comprises an epitope against which mucosal immunity is desired. The methods may be used to immunize an individual against a pathogen infection, hyperproliferative diseases or autoimmune diseases using nucleic acid molecules which encode proteins and peptides that share an epitope with a pathogen antigen or protein associated with cells involved in hyperproliferative diseases or autoimmune diseases, respectively.

L7 ANSWER 6 OF 123 USPATFULL

AN 2002:24372 USPATFULL  
TI Compositions and methods comprising DNA sequences encoding B.  
burgdorferi polypeptides  
IN Flavell, Richard A., Killingworth, CT, United States  
Kantor, Fred S., Orange, CT, United States  
Barthold, Stephen W., Madison, CT, United States  
Fikrig, Erol, Guilford, CT, United States  
PA Yale University, New Haven, CT, United States (U.S. corporation)  
PI US 6344552 B1 20020205  
AI US 1995-455973 19950531 (8)  
RLI Division of Ser. No. US 1994-320161, filed on 7 Oct 1994, now patented,  
Pat. No. US 5747294 Continuation of Ser. No. US 1991-682355, filed on 8  
Apr 1991, now abandoned Continuation-in-part of Ser. No. US 1990-602551,  
filed on 26 Oct 1990, now abandoned Continuation-in-part of Ser. No. US  
1990-538969, filed on 15 Jun 1990, now abandoned

DT Utility  
FS GRANTED

EXNAM Primary Examiner: Bui, Phuong T  
LREP Fish & Neave, Haley, Jr., Esq., James F., Gunnison, Esq., Jane T.

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 2577

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the prevention and diagnosis of Lyme disease. OspA and OspB polypeptides and serotypic variants thereof, which elicit in a treated animal the formation of an immune response which is effective to treat or protect against Lyme disease as caused by infection with \*\*\*Borrelia\*\*\* burgdorferi. Anti-OspA and anti-OspB antibodies that are effective to treat or protect against Lyme disease as caused by infection with B. burgdorferi. A screening method for the selection of those OspA and OspB polypeptides and anti-OspA and anti-OspB antibodies that are useful for the prevention and detection of Lyme disease. Diagnostic kits including OspA and OspB polypeptides or antibodies directed against such polypeptides.

L7 ANSWER 7 OF 123 USPATFULL

AN 2002:19393 USPATFULL

TI Secreted protein HLHFP03

IN Rosen, Craig A., Laytonsville, MD, United States  
Ruben, Steven M., Olney, MD, United States  
Olsen, Henrik S., Gaithersburg, MD, United States  
Ebner, Reinhard, Gaithersburg, MD, United States

PA Human Genome Sciences, Inc., Rockville, MD, United States (U.S.  
corporation)

PI US 6342581 B1 20020129

AI US 1999-227357 19990108 (9)

RLI Continuation-in-part of Ser. No. WO 1998-US13684, filed on 7 Jul 1998

PRAI US 1997-58785 19970912 (60)  
US 1997-58664 19970912 (60)  
US 1997-58660 19970912 (60)  
US 1997-58661 19970912 (60)  
US 1997-55722 19970818 (60)  
US 1997-55723 19970818 (60)  
US 1997-55948 19970818 (60)

US 1997-55949	19970818 (60)
US 1997-55953	19970818 (60)
US 1997-55950	19970818 (60)
US 1997-55947	19970818 (60)
US 1997-55964	19970818 (60)
US 1997-56360	19970818 (60)
US 1997-55684	19970818 (60)
US 1997-55984	19970818 (60)
US 1997-55954	19970818 (60)
US 1997-51926	19970708 (60)
US 1997-52793	19970708 (60)
US 1997-51925	19970708 (60)
US 1997-51929	19970708 (60)
US 1997-52803	19970708 (60)
US 1997-52732	19970708 (60)
US 1997-51931	19970708 (60)
US 1997-51932	19970708 (60)
US 1997-51916	19970708 (60)
US 1997-51930	19970708 (60)
US 1997-51918	19970708 (60)
US 1997-51920	19970708 (60)
US 1997-52733	19970708 (60)
US 1997-52795	19970708 (60)
US 1997-51919	19970708 (60)
US 1997-51928	19970708 (60)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Myers, Carla J.; Assistant Examiner: Spiegler,  
Alexander H.

LREP Human Genome Sciences, Inc.

CLMN Number of Claims: 46

ECL Exemplary Claim: 1

DRWN 0 Drawing Figure(s); 0 Drawing Page(s)

LN.CNT 18742

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

L7 ANSWER 8 OF 123 USPATFULL

AN 2001:233138 USPATFULL

TI \*\*\*Vaccines\*\*\*

IN Friede, Martin, Cardiff, CA, United States  
Garcon, Nathalie, Rixensart, Belgium

PA SmithKline Beecham Biologicals s.a. (U.S. corporation)

PI US 2001053365 A1 20011220

AI US 2001-819464 A1 20010328 (9)

RLI Continuation-in-part of Ser. No. US 1997-945450, filed on 12 Dec 1997,  
ABANDONED A 371 of International Ser. No. WO 1996-EP1464, filed on 1 Apr  
1996, UNKNOWN A 371 of International Ser. No. US 1999-269383, filed on 2  
Apr 1999, ABANDONED A 371 of International Ser. No. WO 1997-EP5578,

filed on 30 Sep 1997, UNKNOWN

PRAI GB 1995-8326 19950425

GB 1996-910019 19960401

GB 1996-20795 19961005

DT Utility

FS APPLICATION

LREP GLAXOSMITHKLINE, Corporate Intellectual Property -UW2220, P. O. Box  
1539, King of Prussia, PA, 19406-0939

CLMN Number of Claims: 49

ECL Exemplary Claim: 1

DRWN 10 Drawing Page(s)

LN.CNT 1397

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a \*\*\*vaccine\*\*\* composition comprising an antigen, an immunologically active saponin fraction and a sterol.

L7 ANSWER 9 OF 123 USPATFULL

AN 2001:218013 USPATFULL

TI Tick antigens and compositions and methods comprising them

IN Kantor, Fred S., Orange, CT, United States

Fikrig, Erol, Guilford, CT, United States

Das, Subrata, New Haven, CT, United States

PI US 2001046499 A1 20011129

AI US 2000-728914 A1 20001201 (9)

PRAI US 1999-169048 19991203 (60)

US 2000-240716 20001016 (60)

DT Utility

FS APPLICATION

LREP FISH & NEAVE, 1251 AVENUE OF THE AMERICAS, 50TH FLOOR, NEW YORK, NY,  
10020-1105

CLMN Number of Claims: 54

ECL Exemplary Claim: 1

DRWN 49 Drawing Page(s)

LN.CNT 3235

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for conferring tick immunity and preventing or reducing the transmission of tick-borne pathogens. Tick polypeptides,

fragments and derivatives; fusion and multimeric proteins comprising the polypeptides, fragments or derivatives; nucleic acid molecules encoding them; antibodies directed against the polypeptides, fusion proteins or multimeric proteins and compositions comprising the antibodies.

\*\*\*Vaccines\*\*\* comprising the polypeptides, fragments or derivatives, alone or in addition to other protective polypeptides. Methods comprising the polypeptides, antibodies and \*\*\*vaccines\*\*\*.

L7 ANSWER 10 OF 123 USPATFULL

AN 2001:212420 USPATFULL

TI Immunostimulatory nucleic acids for inducing a Th2 immune response

IN McCluskie, Michael J., Ottawa, Canada

Davis, Heather L., Ottawa, Canada

PI US 2001044416 A1 20011122

AI US 2001-768012 A1 20010122 (9)

PRAI US 2000-177461 20000120 (60)

DT Utility

FS APPLICATION

LREP Helen Lockhart, c/o Wolf, Greenfield & Sacks, P.C., Federal Reserve Plaza, 600 Atlantic Avenue, Boston, MA, 02210-2211

CLMN Number of Claims: 153

ECL Exemplary Claim: 1

DRWN 14 Drawing Page(s)

LN.CNT 3831

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to methods and products for inducing an immune response using immunostimulatory nucleic acids. In particular the immunostimulatory nucleic acids preferentially induce a Th2 immune response. The invention is useful for treating and preventing disorders associated with a Th1 immune response or for creating a Th2 environment for treating disorders that are sensitive to Th2 immune responses.

L7 ANSWER 11 OF 123 USPATFULL

AN 2001:182096 USPATFULL

TI Autologous immune cell therapy: cell compositions, methods and applications to treatment of human disease

IN Gruenberg, Micheal L., Poway, CA, United States

PI US 2001031253 A1 20011018

AI US 2001-824906 A1 20010402 (9)

RLI Division of Ser. No. US 1996-700565, filed on 25 Jul 1996, PENDING

Division of Ser. No. WO 1996-US12170, filed on 24 Jul 1996, UNKNOWN

PRAI US 1995-44693 19950726 (60)

DT Utility

FS APPLICATION

LREP Stephanie Seidman, Heller Ehrman White & McAuliffe LLP, 4250 Executive Square, 7th Floor, La Jolla, CA, 92037

CLMN Number of Claims: 101

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2692

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions containing clinically-relevant numbers of immune cells that have been isolated from a patient differentiated and/or expanded ex vivo. Methods for treating or preventing disease or otherwise altering the immune status of the patient by reinfusing such cells into the donor are also provided. Methods for expanding and/or immune cells, including effector cells, in the absence of exogenous IL-2, and for administering the cells in the absence of co-infused IL-2 are also provided.

L7 ANSWER 12 OF 123 USPATFULL

AN 2001:176356 USPATFULL

TI Composition and methods for the treatment of cancer and viral infections

IN Patterson, David, Denver, CO, United States

PA Eleanor Roosevelt Institute (U.S. corporation)

PI US 2001029012 A1 20011011

AI US 2001-835597 A1 20010416 (9)

RLI Continuation-in-part of Ser. No. US 2000-534420, filed on 23 Mar 2000,

PENDING

PRAI US 1999-125754 19990323 (60)

DT Utility

FS APPLICATION

LREP Joseph E. Kovarik, Esq., SHERIDAN ROSS P.C., 1560 Broadway, Suite 1200, Denver, CO, 80202-5141

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1408

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds and methods for the treatment of cancer and viral diseases include the administration of viral proteins having substantial homology to BNRF1, FGARAT and/or PRAT. The proteins of the present invention and the nucleic acids encoding such proteins are useful to treat various cancers and uncontrolled cell growth, as well as viral infections, including AIDS. Assays of the present invention are useful in identifying inhibitors of interactions between telomerase, telomeres and viral proteins, especially those that are similar to proteins participating in purine synthesis.

L7 ANSWER 13 OF 123 USPATFULL

AN 2001:155766 USPATFULL

TI 49 human secreted proteins

IN Moore, Paul A., Germantown, MD, United States

Ruben, Steven M., Oley, MD, United States

Olsen, Henrik S., Gaithersburg, MD, United States

Shi, Yanggu, Gaithersburg, MD, United States

Rosen, Craig A., Laytonsville, MD, United States

Florence, Kimberly A., Rockville, MD, United States

Soppet, Daniel R., Centreville, VA, United States

Lafleur, David W., Washington, DC, United States

Endress, Gregory A., Potomac, MD, United States

Ebner, Reinhard, Gaithersburg, MD, United States

Komatsoulis, George, Silver Spring, MD, United States

Duan, Roxanne D., Bethesda, MD, United States

PI US 2001021700 A1 20010913

AI US 2000-739254 A1 20001219 (9)

RLI Continuation of Ser. No. US 2000-511554, filed on 23 Feb 2000, ABANDONED

Continuation-in-part of Ser. No. WO 1999-US19330, filed on 24 Aug 1999,

UNKNOWN

PRAI US 1998-97917 19980825 (60)

US 1998-98634 19980831 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 23

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 15462

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

L7 ANSWER 14 OF 123 USPATFULL

AN 2001:134285 USPATFULL

TI PROGRESSION ELEVATED GENE-3 AND USES THEREOF  
IN FISHER, PAUL B., SCARSDALE, NY, United States  
PI US 2001014734 A1 20010816  
AI US 1998-52753 A1 19980331 (9)  
RLI Continuation-in-part of Ser. No. WO 1998-US5793, filed on 20 Mar 1998,  
UNKNOWN Continuation-in-part of Ser. No. US 1997-821818, filed on 21 Mar  
1997, GRANTED, Pat. No. US 6146877  
DT Utility  
FS APPLICATION  
LREP COOPER & DUNHAM, 1185 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036  
CLMN Number of Claims: 30  
ECL Exemplary Claim: 1  
DRWN 36 Drawing Page(s)  
LN.CNT 5857

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a vector suitable for introduction into a cell, comprising: a) an inducible PEG-3 regulatory region; and b) a gene encoding a product that causes or may be induced to cause the death or inhibition of cancer cell growth. In addition, this invention further provides the above-described vectors, wherein the inducible PEG-3 regulatory region is a promoter. This invention further provides the above-described vectors, wherein the gene encodes an inducer of apoptosis. In addition, this invention provides the above-described vectors, wherein the gene is a tumor suppressor gene. In addition, this invention provides the above-described vectors, wherein the gene encodes a viral replication protein. This invention also provides the above-described vectors, wherein the gene encodes a product toxic to cells or an intermediate to a product toxic to cells. In addition, this invention provides the above-described vectors, wherein the gene encodes a product causing enhanced immune recognition of the cell. This invention further provides the above-described vectors, wherein the gene encodes a product causing the cell to express a specific antigen.

L7 ANSWER 15 OF 123 USPATFULL  
AN 2001:119048 USPATFULL  
TI IMMUNOGENIC CONSTRUCT, PROCESS FOR ITS PREPARATION AND USE AS A \*\*\*VACCINE\*\*\*  
IN MANNHALTER, JOSEF W., VIENNA, Euratom  
LEIBL, HEINZ, VIENNA, Euratom  
EIBL, MARTHA, VIENNA, Euratom  
PI US 2001009669 A1 20010726  
AI US 1997-973397 A1 19971212 (8)  
WO 1996-EP2098 19960515  
None PCT 102(e) date  
PRAI DE 1995-19521705 19950614

DT Utility  
FS APPLICATION  
LREP LISA B. KOLE, BAKER & BOTTS, L.L.P., 30 ROCKEFELLER PLAZA, PO BOX 25696,  
NEW YORK, NY, 10112  
CLMN Number of Claims: 34  
ECL Exemplary Claim: 1  
DRWN 1 Drawing Page(s)  
LN.CNT 698

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns an immunogenic construct comprising as components

(i) an inactive flavivirus or a derivative thereof, and (ii) at least one immunogenic component which is bonded to the flavivirus or adsorbed therewith. The invention further concerns a process for preparing the immunogenic construct and its use as a \*\*\*vaccine\*\*\*.

L7 ANSWER 16 OF 123 USPATFULL

AN 2001:105331 USPATFULL

TI GENETIC \*\*\*VACCINE\*\*\* VECTOR ENGINEERING

IN PUNNONEN, JUHA, PALO ALTO, CA, United States

STEMMER, WILLEM P.C., LOS GATOS, CA, United States

WHALEN, ROBERT G., PARIS, France

HOWARD, RUSSELL, LOS ALTOS HILLS, CA, United States

PI US 2001006950 A1 20010705

AI US 1999-247888 A1 19990210 (9)

PRAI US 1998-74294 19980211 (60)

DT Utility

FS APPLICATION

LREP LAW OFFICES OF JONATHAN ALAN QUINE, P O BOX 458, ALAMEDA, CA, 94501

CLMN Number of Claims: 73

ECL Exemplary Claim: 1

DRWN 20 Drawing Page(s)

LN.CNT 4612

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides methods of obtaining improved genetic \*\*\*vaccines\*\*\* by use of DNA shuffling. Through use of the claimed methods, vectors can be obtained which exhibit increased efficacy for use as genetic \*\*\*vaccines\*\*\*. Improved vectors obtained by using the methods can have, for example, enhanced antigen expression, increased uptake into a cell, increased stability in a cell, ability to tailor an immune response, and the like.

L7 ANSWER 17 OF 123 USPATFULL

AN 2001:226255 USPATFULL

TI Recombinant swinepox virus

IN Cochran, Mark D., Carlsbad, CA, United States

Junker, David E., San Diego, CA, United States

PA Syntro Corporation, San Diego, CA, United States (U.S. corporation)

PI US 6328975 B1 20011211

AI US 1995-375992 19950119 (8)

RLI Continuation-in-part of Ser. No. WO 1994-US8277, filed on 22 Jul 1994

Continuation-in-part of Ser. No. US 1993-97554, filed on 22 Jul 1993,

now patented, Pat. No. US 5869312 Continuation-in-part of Ser. No. US

1992-820154, filed on 13 Jan 1992, now patented, Pat. No. US 5382425

DT Utility

FS GRANTED

EXNAM Primary Examiner: Salimi, Ali R.

LREP Salkeld, Pamela G.

CLMN Number of Claims: 32

ECL Exemplary Claim: 1

DRWN 92 Drawing Figure(s); 92 Drawing Page(s)

LN.CNT 4592

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a recombinant swinepox virus comprising a foreign DNA sequence which is (a) inserted into the swinepox virus genomic DNA, wherein the foreign DNA sequence is inserted within a

region of the genome which corresponds to the 2.0 kb HindIII to BglII subfragment located within the HindIII M fragment of the swinepox virus genome and (b) is expressed in a swinepox virus infected host cell. The invention further provides homology vectors, \*\*\*vaccines\*\*\* and methods of immunization.

L7 ANSWER 18 OF 123 USPATFULL

AN 2001:202202 USPATFULL

TI \*\*\*Borrelia\*\*\* burgdorferi bacterin

IN Korshus, Jon B., Minneapolis, MN, United States  
Runnels, Paul L., Floyd, IA, United States  
Sharpee, Richard L., Green Oaks, IL, United States  
Schell, Ronald F., Madison, WI, United States  
Callister, Steven M., Onalaska, WI, United States

PA Solvay Animal Health, Inc., Mendota Heights, MN, United States (U.S. corporation)

PI US 6316005 B1 20011113

WO 9527504 19951019

AI US 1997-722013 19970121 (8)

WO 1995-US4455 19950411

19970121 PCT 371 date

19970121 PCT 102(e) date

RLI Continuation-in-part of Ser. No. US 1994-226297, filed on 11 Apr 1994,  
now abandoned

DT Utility

FS GRANTED

EXNAM Primary Examiner: Devi, S.

LREP Darby & Darby

CLMN Number of Claims: 38

ECL Exemplary Claim: 1

DRWN 30 Drawing Figure(s); 20 Drawing Page(s)

LN.CNT 3497

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A bacterin including effective immunizing amounts of two non-crossprotective isolates of inactivated \*\*\*Borrelia\*\*\* burgdorferi, an adjuvant in an amount effective to enhance the immunogenicity of the inactivated \*\*\*Borrelia\*\*\* burgdorferi isolates and a suitable carrier is provided herein. The bacterin may also contain a third non-crossprotective isolate. A bacterin including effective immunizing amounts of an antigenic subunit derived from a first \*\*\*Borrelia\*\*\* burgdorferi isolate and a second, non-crossprotective \*\*\*Borrelia\*\*\* burgdorferi isolate, an adjuvant in an amount effective to enhance the immunogenicity of the antigenic subunits and a suitable carrier is also provided. The bacterin may also contain an effective immunizing amount of an antigenic subunit of a third \*\*\*Borrelia\*\*\* burgdorferi. Further provided is a bacterin which includes effective immunizing amounts of two non-crossprotective isolates of inactivated \*\*\*Borrelia\*\*\* burgdorferi and one or more antigenic subunits from the non-crossprotective isolates, an adjuvant in an amount effective to enhance the immunogenicity of the inactivated \*\*\*Borrelia\*\*\* burgdorferi and antigenic subunits and a suitable carrier. Methods of immunizing an animal against \*\*\*Borrelia\*\*\* burgdorferi infection which comprise administering to the animal a dose of a bacterin provided herein are also provided.

L7 ANSWER 19 OF 123 USPATFULL

AN 2001:190752 USPATFULL

TI Therapeutic treatment and prevention of infections with a bioactive materials encapsulated within a biodegradable-biocompatible polymeric matrix

IN Setterstrom, Jean A., Alpharetta, GA, United States  
Van Hamont, John E., Fort Meade, MD, United States  
Reid, Robert H., McComas, CT, United States  
Jacob, Elliot, Silver Spring, MD, United States  
Jeyanthi, Ramasubbu, Columbia, MD, United States  
Boedeker, Edgar C., Chevy Chase, MD, United States  
McQueen, Charles E., Olney, MD, United States  
Jarboe, Daniel L., Silver Spring, MD, United States  
Cassels, Frederick, Ellicott City, MD, United States  
Brown, William, Denver, CO, United States  
Thies, Curt, Ballwin, MO, United States  
Tice, Thomas R., Birmington, AL, United States  
Roberts, F. Donald, Dover, MA, United States  
Friden, Phil, Beford, MA, United States4)

PA The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)

PI US 6309669 B1 20011030

AI US 1997-789734 19970127 (8)

RLI Continuation-in-part of Ser. No. US 1996-590973, filed on 24 Jan 1996, now abandoned Continuation-in-part of Ser. No. US 1995-446149, filed on 22 May 1995, now abandoned Continuation of Ser. No. US 1984-590308, filed on 6 Mar 1984, now abandoned And Ser. No. US 789734  
Continuation-in-part of Ser. No. US 1995-446148, filed on 22 May 1995  
Continuation-in-part of Ser. No. US 1992-867301, filed on 10 Apr 1992, now patented, Pat. No. US 5417986, issued on 23 May 1995  
Continuation-in-part of Ser. No. US 1984-590308, filed on 16 Mar 1984, now abandoned

DT Utility

FS GRANTED

EXNAM Primary Examiner: Harrison, Robert H.

LREP Nash, Caroline, Arwine, Elizabeth

CLMN Number of Claims: 25

ECL Exemplary Claim: 1

DRWN 87 Drawing Figure(s); 85 Drawing Page(s)

LN.CNT 6182

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel burst-free, sustained release biocompatible and biodegradable microcapsules which can be programmed to release their active core for variable durations ranging from 1-100 days in an aqueous physiological environment. The microcapsules are comprised of a core of polypeptide or other biologically active agent encapsulated in a matrix of poly(lactide/glycolide) copolymer, which may contain a pharmaceutically-acceptable adjuvant, as a blend of upcapped free carboxyl end group and end-capped forms ranging in ratios from 100/0 to 1/99.

L7 ANSWER 20 OF 123 USPATFULL

AN 2001:178793 USPATFULL

TI Composition and methods for the treatment of cancer and viral infections

IN Patterson, David, Denver, CO, United States

PA Elenor Roosevelt Institute, Denver, CO, United States (U.S. corporation)

PI US 6303289 B1 20011016

AI US 2000-534420 20000323 (9)

PRAI US 1999-125754 19990323 (60)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Schwartzman, Robert A.; Assistant Examiner: Davis,  
Katharine F

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1493

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds and methods for the treatment of cancer and viral diseases

include the administration of viral proteins having substantial homology  
to BNRF1, FGARAT and/or PRAT. The proteins of the present invention and  
the nucleic acids encoding such proteins are useful to treat various  
cancers and uncontrolled cell growth, as well as viral infections,  
including AIDS. Assays of the present invention are useful in  
identifying inhibitors of interactions between telomerase, telomeres and  
viral proteins, especially those that are similar to proteins  
participating in purine synthesis.

L7 ANSWER 21 OF 123 USPATFULL

AN 2001:178639 USPATFULL

TI Production of \*\*\*borrelia\*\*\* burgdorferi \*\*\*vaccine\*\*\* , product  
produced thereby and method of use

IN Alliger, Howard M., Melville, NY, United States  
Frey, Alan, Highland Park, NJ, United States

PA Rx Technologies, Melville, NY, United States (U.S. corporation)

PI US 6303129 B1 20011016

AI US 1995-475542 19950607 (8)

RLI Division of Ser. No. US 1992-921303, filed on 28 Jul 1992, now patented,  
Pat. No. US 5582829

DT Utility

FS GRANTED

EXNAM Primary Examiner: Minnifield, Nita

LREP Coleman, Henry D., Sudol, R. Neil, Sapone, William J.

CLMN Number of Claims: 26

ECL Exemplary Claim: 1

DRWN 7 Drawing Figure(s); 7 Drawing Page(s)

LN.CNT 1186

AB A process for the preparation of a \*\*\*vaccine\*\*\* from substantially  
viable spirochetal bacteria of \*\*\*Borrelia\*\*\* , preferably

\*\*\*Borrelia\*\*\* burgdorferi having immunogenic or therapeutic  
properties and capable of inducing an immune or therapeutic response  
against Lyme Disease when administered to a patient is described. The  
product for use against Lyme Disease is produced by ultrasound treatment  
of substantially viable spirochetal bacteria of \*\*\*Borrelia\*\*\*  
burgdorferi. The invention produces a product and a method of treatment  
that can be used for the immunization and/or therapy of a patient  
against Lyme Disease to minimize or prevent the contraction of the  
disease or to treat the disease.

L7 ANSWER 22 OF 123 USPATFULL

AN 2001:162850 USPATFULL  
TI Recombinant raccoonpox virus and uses thereof as a \*\*\*vaccine\*\*\* in mammalian and avian species  
IN Cochran, Mark D., Carlsbad, CA, United States  
Junker, David E., San Diego, CA, United States  
PA Schering-Plough Veterinary Corp., Reno, NV, United States (U.S. corporation)  
PI US 6294176 B1 20010925  
AI US 1998-113750 19980710 (9)  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Salimi, Ali R.  
LREP Salkeld, Pamela G., Zaradic, Sandy S.  
CLMN Number of Claims: 24  
ECL Exemplary Claim: 1  
DRWN 9 Drawing Figure(s); 9 Drawing Page(s)  
LN.CNT 2882  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a recombinant raccoonpox virus comprising a raccoonpox virus viral genome which contains a foreign DNA sequence inserted into a non-essential region within the HindIII "U" genomic region, the HindIII "M" genomic region, or HindIII "N" genomic region of the raccoonpox virus genome. The present invention provides a recombinant raccoonpox virus comprising a raccoonpox virus viral genome which contains a deletion in a raccoonpox virus host range gene of the viral genome. The present invention provides a homology vector for producing a recombinant raccoonpox virus by inserting a foreign DNA sequence into the raccoonpox virus genome. The present invention provides a recombinant raccoonpox virus which is useful as a \*\*\*vaccine\*\*\* in mammalian and avian species.

L7 ANSWER 23 OF 123 USPATFULL  
AN 2001:117167 USPATFULL  
TI Nucleic acid constructs whose activity is affected by inhibitors of cyclin-dependent kinases and uses thereof  
IN Eilers, Martin, Marburg, Germany, Federal Republic of  
Buergin, Andrea, Marburg, Germany, Federal Republic of  
Sedlacek, Hans-Harald, Marburg, Germany, Federal Republic of  
PA Aventis Pharma Deutschland GmbH, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)  
PI US 6265562 B1 20010724  
AI US 1998-215221 19981218 (9)  
PRAI DE 1997-19756975 19971220  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Hauda, Karen M.; Assistant Examiner: Woitach, Joseph T.  
CLMN Number of Claims: 28  
ECL Exemplary Claim: 1  
DRWN 25 Drawing Figure(s); 25 Drawing Page(s)  
LN.CNT 2413

CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB The present application discloses nucleic acid constructs comprising nucleic acids which encode a protein which inhibits the cellular protein p27 and thereby relieves the inhibition of the proliferation of the cell

which is brought about by p27, fragments and variants thereof, some of which possess a dominant interfering character.

L7 ANSWER 24 OF 123 USPATFULL

AN 2001:97430 USPATFULL

TI Immunological combination compositions and methods

IN Becker, Robert S., Henryville, PA, United States

Huebner, Robert C., Stroudsburg, PA, United States

Gray, Maryann B., Bartonsville, PA, United States

Biscardi, Karen S., South Sterling, PA, United States

PA Connaught Laboratories, Inc., Swiftwater, PA, United States (U.S. corporation)

PI US 6251405 B1 20010626

AI US 1995-476656 19950607 (8)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Swart, Rodney P.

LREP McDonnell Boehnen Hulbert & Berghoff

CLMN Number of Claims: 11

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 1274

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Immunological compositions and methods for making and using them. The

compositions contain an antigen and a lipoprotein and optionally an adjuvant. The lipoprotein can itself be antigenic or immunoactive. The antigen can be influenza HA and the lipoprotein a recombinantly expressed product having an OspA leader for lipidation and PspA for the protein portion. The antigen can be OspC and the lipoprotein OspA. The components of the composition are co-administered. A potentiated immunological response is obtained by the compositions and methods.

L7 ANSWER 25 OF 123 USPATFULL

AN 2001:97428 USPATFULL

TI Recombinant swinepox virus

IN Cochran, Mark D., Carlsbad, CA, United States

Junker, David E., San Diego, CA, United States

PA Syntro Corporation, Lenexa, KS, United States (U.S. corporation)

PI US 6251403 B1 20010626

AI US 1995-488237 19950607 (8)

RLI Continuation-in-part of Ser. No. US 1995-375992, filed on 19 Jan 1995

Continuation-in-part of Ser. No. WO 1994-US8277, filed on 22 Jul 1994

Continuation-in-part of Ser. No. US 1993-97554, filed on 22 Jul 1993,

now patented, Pat. No. US 5869312 Continuation-in-part of Ser. No. US

1992-820154, filed on 13 Jan 1992, now patented, Pat. No. US 5382425

DT Utility

FS GRANTED

EXNAM Primary Examiner: Salimi, Ali

LREP White, John P. Cooper & Dunham LLP

CLMN Number of Claims: 21

ECL Exemplary Claim: 1,4

DRWN 114 Drawing Figure(s); 114 Drawing Page(s)

LN.CNT 6042

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a recombinant swinepox virus comprising a

foreign DNA sequence inserted into the swinepox virus genomic DNA, wherein the foreign DNA sequence is inserted within a HindIII M fragment of the swinepox virus genomic DNA and is capable of being expressed in a swinepox virus infected host cell. The invention further provides homology vectors, \*\*\*vaccines\*\*\* and methods of immunization.

L7 ANSWER 26 OF 123 USPATFULL

AN 2001:93325 USPATFULL

TI Sequence and method for genetic engineering of proteins with cell membrane translocating activity

IN Lin, Yao-Zhong, Nashville, TN, United States  
Donahue, John P., Nashville, TN, United States  
Rojas, Mauricio, Nashville, TN, United States  
Tan, Zhong-Jia, Nashville, TN, United States

PA Vanderbilt University, Nashville, TN, United States (U.S. corporation)

PI US 6248558 B1 20010619

AI US 1998-186170 19981104 (9)

PRAI US 1998-80083 19980331 (60)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Carlson, Karen Cochrane; Assistant Examiner:

Srivastava, Devesh

LREP Needle & Rosenberg, P.C.

CLMN Number of Claims: 32

ECL Exemplary Claim: 1

DRWN 15 Drawing Figure(s); 9 Drawing Page(s)

LN.CNT 1376

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention describes a membrane-translocating peptide sequence (MTS) which facilitates entry of polypeptides and proteins into cells. Also described is an isolated nucleotide sequence encoding the membrane-translocating peptide and a method of using this sequence to genetically engineer proteins with cell membrane permeability. The MTS, and the method of genetically engineering proteins with cell membrane permeability, are useful for polypeptide and protein delivery for human and veterinary applications such as \*\*\*vaccine\*\*\* delivery and cancer therapy.

L7 ANSWER 27 OF 123 USPATFULL

AN 2001:82308 USPATFULL

TI Method for treating brain cancer with a conditionally lethal gene

IN Barber, Jack R., San Diego, CA, United States  
Gruber, Harry E., San Diego, CA, United States  
Jolly, Douglas J., Leucadia, CA, United States

PA Chiron Corporation, Emeryville, CA, United States (U.S. corporation)

PI US 6241982 B1 20010605

AI US 1995-468646 19950606 (8)

RLI Division of Ser. No. US 1993-155944, filed on 18 Nov 1993, now abandoned  
Continuation-in-part of Ser. No. US 1993-139994, filed on 20 Oct 1993,  
now abandoned Continuation of Ser. No. US 1992-965084, filed on 22 Oct  
1992, now abandoned Continuation of Ser. No. US 1990-586603, filed on 21  
Sep 1990, now abandoned Continuation-in-part of Ser. No. US 1990-565606,  
filed on 10 Aug 1990, now abandoned Continuation-in-part of Ser. No. US  
1989-395932, filed on 18 Aug 1989, now abandoned Continuation-in-part of  
Ser. No. US 1988-170515, filed on 21 Mar 1988, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Schwartzman, Robert A.

LREP Pochopien, Donald, Dollard, Anne, Blackburn, Robert

CLMN Number of Claims: 34

ECL Exemplary Claim: 1

DRWN 30 Drawing Figure(s); 25 Drawing Page(s)

LN.CNT 2796

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides recombinant viral vectors carrying a vector construct which directs the expression of a gene product (e.g., HSVTK) that activates a compound with little or no cytotoxicity into a toxic product. Also provided are methods of destroying or inhibiting pathogenic agents in a warm blooded animal, comprising the step of administering to the animal a viral vector such as that described above, in order to inhibit or destroy the pathogenic agent.

L7 ANSWER 28 OF 123 USPATFULL

AN 2001:71101 USPATFULL

TI Strategically modified hepatitis B core proteins and their derivatives

IN Birkett, Ashley J., Solana Beach, CA, United States

PA Immune Complex Corporation, San Diego, CA, United States (U.S. corporation)

PI US 6231864 B1 20010515

AI US 1999-248588 19990211 (9)

PRAI US 1998-74537 19980212 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Wortman, Donna C.

LREP Welsh & Katz, Ltd.

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 1665

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A strategically modified hepatitis B core protein is described, where an insert is provided, preferably in an immunodominant region of the nucleocapsid protein, containing a chemically reactive amino acid residue. The modified hepatitis B core protein or its aggregated nucleocapsid protein particles can be pendently linked to a hapten to form a modified nucleocapsid conjugate. Such a conjugate is useful in the preparation of \*\*\*vaccines\*\*\* or antibodies. The modified hepatitis B core protein can also be modified to include a T cell epitope.

L7 ANSWER 29 OF 123 USPATFULL

AN 2001:67794 USPATFULL

TI Human respiratory syncytial virus peptides with antifusogenic and antiviral activities

IN Barney, Shawn O'Lin, Cary, NC, United States

Lambert, Dennis Michael, Cary, NC, United States

Petteway, Stephen Robert, Cary, NC, United States

PA Trimeris, Inc., Durham, NC, United States (U.S. corporation)

PI US 6228983 B1 20010508

AI US 1995-485264 19950607 (8)

RLI Division of Ser. No. US 1995-470896, filed on 6 Jun 1995  
Continuation-in-part of Ser. No. US 1994-360107, filed on 20 Dec 1994  
Continuation-in-part of Ser. No. US 1994-255208, filed on 7 Jun 1994  
Continuation-in-part of Ser. No. US 1993-73028, filed on 7 Jun 1993, now  
patented, Pat. No. US 5464933

DT Utility

FS Granted

EXNAM Primary Examiner: Scheiner, Laurie; Assistant Examiner: Parkin, Jeffrey  
S.

LREP Pennie & Edmonds LLP

CLMN Number of Claims: 62

ECL Exemplary Claim: 1

DRWN 84 Drawing Figure(s); 83 Drawing Page(s)

LN.CNT 32166

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to peptides which exhibit antifusogenic and antiviral activities. The peptides of the invention consist of a 16 to 39 amino acid region of a human respiratory syncytial virus protein. These regions were identified through computer algorithms capable of recognizing the ALLMOT15, 107x178x4, or PLZIP amino acid motifs. These motifs are associated with the antifusogenic and antiviral activities of the claimed peptides.

L7 ANSWER 30 OF 123 USPATFULL

AN 2001:59387 USPATFULL

TI \*\*\*Vaccine\*\*\* for the prevention of lyme disease

IN Livey, Ian, Vienna, Austria

Dorner, Friedrich, Vienna, Austria

PA Baxter Aktiengesellschaft, Vienna, Austria (non-U.S. corporation)

PI US 6221363 B1 20010424

AI US 1992-903580 19920625 (7)

RLI Continuation-in-part of Ser. No. US 1992-824161, filed on 22 Jan 1992,  
now abandoned Continuation-in-part of Ser. No. US 1991-727245, filed on  
11 Jul 1991, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Duffy, Patricia A.; Assistant Examiner: Portner, Ginny  
Allen

LREP Foley & Lardner

CLMN Number of Claims: 18

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 1069

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An effective immunogen against Lyme \*\*\*borreliosis\*\*\* in mammals  
comprises homogenous *B. burgdorferi* pC protein and a  
physiologically-acceptable excipient.

L7 ANSWER 31 OF 123 USPATFULL

AN 2001:59385 USPATFULL

TI Recombinant swinepox virus

IN Cochran, Mark D., Carlsbad, CA, United States

Junker, David E., San Diego, CA, United States

PA Syntro Corporation, Lenexa, KS, United States (U.S. corporation)

PI US 6221361 B1 20010424

AI US 1996-686968 19960725 (8)  
RLI Continuation-in-part of Ser. No. WO 1996-US1485, filed on 19 Jan 1996  
Continuation-in-part of Ser. No. US 1995-472679, filed on 7 Jun 1995  
Continuation-in-part of Ser. No. US 1995-488237, filed on 7 Jun 1995  
Continuation-in-part of Ser. No. US 1995-480640, filed on 7 Jun 1995,  
now patented, Pat. No. US 6033904 Continuation-in-part of Ser. No. US  
1995-375992, filed on 19 Jan 1995 , said Ser. No. US 472679  
Continuation-in-part of Ser. No. US 1995-375992, filed on 19 Jan 1995 ,  
said Ser. No. US 488237 Continuation-in-part of Ser. No. US 1995-375992,  
filed on 19 Jan 1995 , said Ser. No. US 480640 Continuation-in-part of  
Ser. No. US 375992

DT Utility

FS Granted

EXNAM Primary Examiner: Mosher, Mary E.

LREP White, John P.Cooper & Dunham LLP

CLMN Number of Claims: 44

ECL Exemplary Claim: 1

DRWN 55 Drawing Figure(s); 55 Drawing Page(s)

LN.CNT 7695

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a recombinant swinepox virus comprising a foreign DNA inserted into a swinepox virus genomic DNA, wherein the foreign DNA is inserted into an EcoRI site within the approximately 3.2 Kb subfragment of the HindIII K fragment of the swinepox virus genomic DNA and is capable of being expressed in a swinepox virus infected host cell. The invention further provides a recombinant swinepox virus designated S-SPV-120, S-SPV-121, S-SPV-122, S-SPV-127, and S-SPV-128. The invention further provides \*\*\*vaccines\*\*\* and methods of immunization of the recombinant swinepox virus.

L7 ANSWER 32 OF 123 USPATFULL

AN 2001:40233 USPATFULL

TI 66 kDa antigen from \*\*\*Borrelia\*\*\*

IN Bergstrom, Sven, Umea, Sweden

Barbour, Alan George, Irvine, CA, United States

PA Symbicom Aktiebolag, Umea, Sweden (non-U.S. corporation)

PI US 6204018 B1 20010320

WO 9535379 19951228

AI US 1997-750494 19970612 (8)

WO 1995-US7665 19950619

19970612 PCT 371 date

19970612 PCT 102(e) date

RLI Continuation-in-part of Ser. No. US 1994-262220, filed on 20 Jun 1994,  
now patented, Pat. No. US 6054296

DT Utility

FS Granted

EXNAM Primary Examiner: Minnifield, Nita M.

LREP Frommer Lawrence & Haug LLP, Frommer, William S., Kolawski, Thomas J.

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN 5 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 2159

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Nucleic acid fragments are disclosed which encode a polypeptide antigen reactive with antisera from rabbits immunised with a 66 kDa protein from

\*\*\*Borrelia\*\*\* garinii IP90. The presence of nucleic acid fragments encoding such a polypeptide antigen as well as the presence of the polypeptide antigen have been demonstrated in three strains of B. burgdorferi sensu lato, but are substantially absent from at least 95% of randomly selected B. hermsii, B. crocidurae, B. anserina, and B. hispanica. The encoded polypeptide is surface exposed on the bacterial surface, it is highly conserved, and is thus potentially useful as a \*\*\*vaccine\*\*\* agent and as a diagnostic agent in the diagnosis of infections with B. burgdorferi as are the characteristic nucleic acid fragments of the invention. Also disclosed are methods of producing the polypeptide antigen according to the invention as are antibodies directed against the antigen.

L7 ANSWER 33 OF 123 USPATFULL

AN 2001:40014 USPATFULL

TI \*\*\*Borrelia\*\*\* antigen

IN Bergstrom, Sven, Umea, Sweden

Barbour, Alan G., San Antonio, TX, United States

Magnarelli, Louis A., Durham, CT, United States

PA Symbicom Aktiebolag, Umea, Sweden (non-U.S. corporation)

PI US 6203798 B1 20010320

AI US 1995-470627 19950606 (8)

RLI Division of Ser. No. US 1993-79601, filed on 23 Jun 1993, now patented, Pat. No. US 5523089 Continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now abandoned Continuation of Ser. No. US 1989-422881, filed on 18 Oct 1989, now abandoned

PRAI DK 1988-5902 19881024

DT Utility

FS Granted

EXNAM Primary Examiner: Swartz, Rodney P.

LREP Frommer Lawrence & Haug LLP, Frommer, William S., Kowalski, Thomas J.

CLMN Number of Claims: 23

ECL Exemplary Claim: 1

DRWN 24 Drawing Figure(s); 24 Drawing Page(s)

LN.CNT 2650

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed and claimed are: substantially pure lipidated OspA protein, compositions containing substantially pure lipidated OspA protein, immunogenic fragments of OspA, compositions containing immunogenic fragments of OspA, polypeptides containing an immunogenic fragment or epitopic region of OspA, and methods for making and using such proteins, fragments, and polypeptides.

L7 ANSWER 34 OF 123 USPATFULL

AN 2001:33252 USPATFULL

TI Compositions and methods for delivery of genetic material

IN Carrano, Richard A., Paoli, PA, United States

Wang, Bin, Haidian, China

Weiner, David B., Merion, PA, United States

PA The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)

Apollan, Inc., Malvern, PA, United States (U.S. corporation)

PI US 6197755 B1 20010306

AI US 1999-321461 19990527 (9)

RLI Continuation of Ser. No. US 704701, now patented, Pat. No. US 5962428

Continuation of Ser. No. US 1994-221579, filed on 1 Apr 1994, now patented, Pat. No. US 5739118, issued on 14 Apr 1998

DT Utility

FS Granted

EXNAM Primary Examiner: Schwartzman, Robert A.

LREP Woodcock Washburn Kurtz Mackiewicz & Norris LLP

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 3329

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of introducing genetic material into cells of an individual and compositions and kits for practicing the same are disclosed. The methods comprise the steps of contacting cells of an individual with a genetic \*\*\*vaccine\*\*\* facilitator and administering to the cells, a nucleic acid molecule that is free of retroviral particles. The nucleic acid molecule comprises a nucleotide sequence that encodes a protein that comprises at least one epitope that is identical or substantially similar to an epitope of a pathogen antigen or an antigen associated with a hyperproliferative or autoimmune disease, a protein otherwise missing from the individual due to a missing, non-functional or partially functioning gene, or a protein that produce a therapeutic effect on an individual. Methods of prophylactically and therapeutically immunizing an individual against HIV are disclosed. Pharmaceutical compositions and kits for practicing methods of the present invention are disclosed.

L7 ANSWER 35 OF 123 USPATFULL

AN 2001:32799 USPATFULL

TI Compositions and methods for the prevention and diagnosis of Lyme disease

IN Flavell, Richard A., Killingworth, CT, United States

Kantor, Fred S., Orange, CT, United States

Barthold, Stephen W., Madison, CT, United States

Fikrig, Erol, Guilford, CT, United States

PA Yale University, New Haven, CT, United States (U.S. corporation)

PI US 6197301 B1 20010306

AI US 1995-455829 19950531 (8)

RLI Division of Ser. No. US 1994-320161, filed on 7 Oct 1994, now patented, Pat. No. US 5747294 Continuation of Ser. No. US 1991-682355, filed on 8 Apr 1991, now abandoned Continuation-in-part of Ser. No. US 1990-602551, filed on 26 Oct 1990, now abandoned Continuation-in-part of Ser. No. US 1990-538969, filed on 15 Jun 1990, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Bui, Phuong T.

LREP Fish & Neave, Haley, Jr., Esq., James F., Gunnison, Esq., Jane T.

CLMN Number of Claims: 86

ECL Exemplary Claim: 7

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 2506

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the prevention and diagnosis of Lyme disease. OspA and OspB polypeptides and serotypic variants thereof, which elicit in a treated animal the formation of an immune response

which is effective to treat or protect against Lyme disease as caused by infection with *B. burgdorferi*. Anti-OspA and anti-OspB antibodies that are effective to treat or protect against Lyme disease as caused by infection with *B. burgdorferi*. A screening method for the selection of those OspA and OspB polypeptides and anti-OspA and anti-OspB antibodies that are useful for the prevention and detection of Lyme disease. Diagnostic kits including OspA and OspB polypeptides or antibodies directed against such polypeptides.

L7 ANSWER 36 OF 123 USPATFULL

AN 2001:18233 USPATFULL

TI OspA DNA and lyme disease \*\*\*vaccine\*\*\*

IN Bergstrom, Sven, Umea, Sweden

Barbour, Alan G., San Antonio, TX, United States

Magnarelli, Louis A., Durham, CT, United States

PA Symbicomb Aktiebolag, Umea, Sweden (non-U.S. corporation)

PI US 6183986 B1 20010206

AI US 1995-466393 19950606 (8)

RLI Division of Ser. No. US 1993-79601, filed on 22 Jun 1993, now patented, Pat. No. US 5523089 Continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now abandoned Continuation of Ser. No. US 1989-422881, filed on 18 Oct 1989, now abandoned

PRAI DK 1988-5902 19881024

DT Utility

FS Granted

EXNAM Primary Examiner: Housel, James; Assistant Examiner: Hines, Ja-Na A.

LREP Frommer Lawrence & Haug, Frommer, William S., Kowalski, Thomas J.

CLMN Number of Claims: 55

ECL Exemplary Claim: 1

DRWN 23 Drawing Figure(s); 24 Drawing Page(s)

LN.CNT 2565

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed and claimed is an isolated DNA molecule having a nucleotide sequence encoding substantially pure OspA, as well as vectors containing such DNA, uses of such DNA, and compositions containing such vectors.

L7 ANSWER 37 OF 123 USPATFULL

AN 2001:18001 USPATFULL

TI Recombinant chimeric virus and uses thereof

IN Cochran, Mark D., Carlsbad, CA, United States

Wild, Martha A., San Diego, CA, United States

Winslow, Barbara J., Delmar, CA, United States

PA Schering-Plough Veterinary Corp., Reno, NV, United States (U.S. corporation)

PI US 6183753 B1 20010206

AI US 1997-804372 19970221 (8)

RLI Continuation-in-part of Ser. No. US 1996-663566, filed on 13 Jun 1996, now patented, Pat. No. US 5853733 Continuation-in-part of Ser. No. WO 1995-US10245, filed on 9 Aug 1995 Continuation-in-part of Ser. No. US 1994-288065, filed on 9 Aug 1994, now patented, Pat. No. US 5961982

DT Utility

FS Granted

EXNAM Primary Examiner: Salimi, Ali

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 3184

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a recombinant herpesvirus of turkeys-Marek's disease virus chimera comprising a herpesvirus of turkeys unique long viral genome region and a Marek's disease virus unique short viral genome region.

L7 ANSWER 38 OF 123 USPATFULL

AN 2001:13969 USPATFULL

TI \*\*\*Vaccine\*\*\* delivery system

IN Stein, Daniel C., Silver Spring, MD, United States

Stover, Charles K., Mercer Island, WA, United States

PA University of Maryland, College Park, MD, United States (U.S. corporation)

PI US 6180111 B1 20010130

AI US 1998-81576 19980519 (9)

RLI Continuation-in-part of Ser. No. US 1997-936522, filed on 23 Sep 1997, now abandoned Continuation of Ser. No. US 1995-443514, filed on 18 May 1995, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Graser, Jennifer

LREP Long Aldridge & Norman

CLMN Number of Claims: 19

ECL Exemplary Claim: 1

DRWN 11 Drawing Figure(s); 9 Drawing Page(s)

LN.CNT 1298

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a hyperblebbing strain of *Neisseria gonorrhoeae* which produces large amounts of blebs useful for production of blebosomes containing antigens for use as a \*\*\*vaccine\*\*\* delivery vehicle or as a diagnostic reagent. The invention also relates to a method for producing high levels of a desired protein in purified form using the hyperblebbing strain of *N. gonorrhoeae*, and to a \*\*\*vaccine\*\*\* delivery systems containing the blebosomes expressing the desired antigen.

L7 ANSWER 39 OF 123 USPATFULL

AN 2001:10718 USPATFULL

TI Antigen carbohydrate compounds and their use in immunotherapy

IN McKenzie, Ian F. C., Victoria, Australia

Apostolopoulos, Vasso, Victoria, Australia

Pietersz, Geoff Allan, Victoria, Australia

PA Austin Research Institute, Victoria, Australia (non-U.S. corporation)

PI US 6177256 B1 20010123

AI US 1998-223043 19981230 (9)

RLI Continuation of Ser. No. US 1997-833807, filed on 9 Apr 1997, now patented, Pat. No. US 5989552 Continuation of Ser. No. US 1994-340711, filed on 16 Nov 1994, now abandoned

PRAI AU 1993-3223 19931226

DT Utility

FS Granted

EXNAM Primary Examiner: Park, Hankyel

LREP Dann Dorfman Herrell and Skillman, P.C.

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN 23 Drawing Figure(s); 10 Drawing Page(s)

LN.CNT 1427

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Conjugates between one or more repeated subunits of an antigen and a carbohydrate polymer are desired. Also described are immunogenic \*\*\*vaccines\*\*\* against disease states which contain the conjugates and methods for inducing cell-mediated immune responses. The conjugates may especially contain polymers of the carbohydrate mannose and one or more repeated subunits of human mucin.

L7 ANSWER 40 OF 123 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2001:527295 BIOSIS

DN PREV200100527295

TI Characterization of a \*\*\*Borrelia\*\*\* burgdorferi VlsE invariable region useful in canine Lyme disease serodiagnosis by enzyme-linked immunosorbent assay.

AU Liang, Fang Ting; Jacobson, Richard H.; Straubinger, Reinhard K.; Grooters, Amy; Philipp, Mario T. (1)

CS (1) Tulane Regional Primate Research Center, Tulane University Health Sciences Center, 18703 Three Rivers Rd., Covington, LA, 70433:  
philipp@tpc.tulane.edu USA

SO Journal of Clinical Microbiology, (November, 2001) Vol. 38, No. 11, pp. 4160-4166. print.

ISSN: 0095-1137.

DT Article

LA English

SL English

AB Sera collected from dogs experimentally infected with \*\*\*Borrelia\*\*\* burgdorferi by tick inoculation were analyzed for an antibody response to each of the six invariable regions (IRs; i.e., IR1 to IR6) of VlsE, the variable \*\*\*surface\*\*\* \*\*\*antigen\*\*\* of *B. burgdorferi*. Six synthetic peptides (C1 to C6), which reproduced the six IR sequences were used as peptide-based, enzyme-linked immunosorbent assay (ELISA) antigens. Two IRs, IR2 and IR6, were found to be immunodominant. Studies with serially collected serum samples from experimentally infected dogs revealed that the antibody response to IR6 appears earlier and is stronger than that to IR2. Thus, the IR6 sequence alone appeared to be sufficient for serodiagnosis. When C6 alone was used as antigen, the peptide-based ELISA was positive in 7 of 23 dogs (30%) as early as 3 weeks postinfection. All dogs (n = 33) became strongly positive 1 or 2 weeks later, and this response persisted for the entire study, which lasted for 69 weeks. Of 55 sera submitted by veterinarians from dogs suspected of having Lyme disease, 19 were also positive by the C6 ELISA, compared to 20 positives detected by immunoblot analysis using cultured *B. burgdorferi* lysates as antigen. The sensitivity of using C2 and C6 together for detecting specific antibody in both experimentally infected and clinically diagnosed dogs was not better than sensitivity with C6 alone, confirming that C6 suffices as a diagnostic probe. Moreover, the C6 ELISA yielded 100% specificity with serum samples collected from 70 healthy dogs, 14 dogs with infections other than *B. burgdorferi*, and 15 animals vaccinated with either outer surface protein A, whole-spirochete \*\*\*vaccines\*\*\*, or the common puppy- \*\*\*vaccines\*\*\*. Therefore, this C6 ELISA was both sensitive and specific for the serodiagnosis of canine Lyme disease and

could be used with vaccinated dogs.

L7 ANSWER 41 OF 123 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

DUPLICATE 1

AN 2001:187806 BIOSIS

DN PREV200100187806

TI C-terminal invariable domain of VlsE may not serve as target for protective immune response against \*\*\**Borrelia*\*\*\* *burgdorferi*.

AU Liang, Fant Ting; Jacobs, Mary B.; Philipp, Mario T. (1)

CS (1) Tulane Regional Primate Research Center, Tulane University Health Sciences Center, 18703 Three Rivers Rd., Covington, LA, 70433:

philipp@tpc.tulane.edu USA

SO Infection and Immunity, (March, 2001) Vol. 69, No. 3, pp. 1337-1343.

print.

ISSN: 0019-9567.

DT Article

LA English

SL English

AB VlsE, the variable \*\*\*surface\*\*\* \*\*\*antigen\*\*\* of the Lyme disease spirochete, \*\*\**Borrelia*\*\*\* *burgdorferi*, contains two invariable domains, at the amino and carboxyl termini, respectively, which collectively account for approximately one-half of the entire molecule's length and remain unchanged during antigenic variation. It is not known if these two invariable domains are exposed at the surface of either the antigen or the spirochete. If they are exposed at the spirochete's surface, they may elicit a protective immune response against *B. burgdorferi* and serve as \*\*\*vaccine\*\*\* candidates. In this study, a 51-mer synthetic peptide that reproduced the entire sequence of the C-terminal invariable domain of VlsE was conjugated to the carrier keyhole limpet hemocyanin and used to immunize mice. Generated mouse antibody was able to immunoprecipitate native VlsE extracted from cultured *B. burgdorferi* B31 spirochetes, indicating that the C-terminal invariable domain was exposed at the antigen's surface. However, this domain was inaccessible to antibody binding at the surface of cultured intact spirochetes, as demonstrated by both an immunofluorescence experiment and an in vitro killing assay. Mouse antibody to the C-terminal invariable domain was not able to confer protection against *B. burgdorferi* infection, indicating that this domain was unlikely exposed at the spirochete's surface *in vivo*. We concluded that the C-terminal invariable domain was exposed at the antigen's surface but not at the surface of either cultured or *in vivo* spirochetes and thus cannot elicit protection against *B. burgdorferi* infection.

L7 ANSWER 42 OF 123 USPATFULL

AN 2000:174364 USPATFULL

TI Parasitic helminth asparaginase proteins, nucleic acid molecules, and uses thereof

IN Chandrashekhar, Ramaswamy, Fort Collins, CO, United States  
Tsuji, Naotoshi, Fort Collins, CO, United States

PA Heska Corporation, United States (U.S. corporation)  
Colorado State University Research Foundation, United States (U.S. corporation)

PI US 6165735 20001226

AI US 1999-397979 19990916 (9)

RLI Division of Ser. No. US 1998-140177, filed on 25 Aug 1998, now patented,

Pat. No. US 6042825 which is a division of Ser. No. US 1997-929501,  
filed on 15 Sep 1997, now patented, Pat. No. US 5854051

DT Utility

FS Granted

EXNAM Primary Examiner: Chan, Christina Y.; Assistant Examiner: Ewoldt, Gerald R.

LREP Heska Corporation

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 3085

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to: parasitic helminth asparaginase proteins; parasitic helminth asparaginase nucleic acid molecules, including those that encode such asparaginase proteins; antibodies raised against such asparaginase proteins; and compounds that inhibit parasitic helminth asparaginase activity. The present invention also includes methods to obtain such proteins, nucleic acid molecules, antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to protect animals from diseases caused by parasitic helminths.

L7 ANSWER 43 OF 123 USPATFULL

AN 2000:164325 USPATFULL

TI Truncated transcriptionally active cytomegalovirus promoters

IN Fischer, Laurent, Albany, NY, United States

PA Merial, Lyons, France (non-U.S. corporation)

PI US 6156567 20001205

AI US 1996-675556 19960703 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Eisenschenk, Frank C.; Assistant Examiner: Bui, Phuong T.

LREP Frommer Lawerence & Haug, LLP, Frommer, William S., Kowalski, Thomas J.

CLMN Number of Claims: 15

ECL Exemplary Claim: 1

DRWN 98 Drawing Figure(s); 97 Drawing Page(s)

LN.CNT 7757

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Recombinant adenoviruses, methods of making them, uses for them, including in immunological, immunogenic, \*\*\*vaccine\*\*\* or therapeutic compositions, or, as a vector for cloning, replicating or expressing DNA and methods of using the compositions and vector, expression products from them, and uses for the expression products are provided. More particularly, recombinant canine adenoviruses (CAV) and methods of making them, uses for them, expression products from them, and uses for the expression products, including recombinant CAV2 viruses are provided. Additionally, truncated promoters, expression cassettes containing the promoters, and recombinant viruses and plasmids containing the promoters or expression cassettes are provided.

L7 ANSWER 44 OF 123 USPATFULL

AN 2000:160592 USPATFULL

TI \*\*\*Borrelia\*\*\* burgdorferi outer membrane proteins  
IN Skare, Jonathan T., College Station, TX, United States  
Shang, Ellen S., Calabasas, CA, United States  
Champion, Cheryl I., Los Angeles, CA, United States  
Blanco, David R., Calabassas, CA, United States  
Miller, James N., Northridge, CA, United States  
Lovett, Michael A., Los Angeles, CA, United States  
Mirzabekov, Tajib A., Newton, MA, United States  
Kagan, Bruce L., Pacific Palisades, CA, United States  
Tempst, Paul, New York, NY, United States  
Foley, Denise M., Orange, CA, United States

PA The Regents of the University of California, Oakland, CA, United States  
(U.S. corporation)

PI US 6153194 20001128

AI US 1998-183217 19981029 (9)

RLI Continuation of Ser. No. US 1997-787367, filed on 21 Jan 1997, now  
abandoned

PRAI US 1996-10321 19960122 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Ryan, V.

LREP Fulbright & Jaworski L.L.P.

CLMN Number of Claims: 5

ECL Exemplary Claim: 1

DRWN 43 Drawing Figure(s); 24 Drawing Page(s)

LN.CNT 3234

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention presents three *B. burgdorferi* membrane proteins: Oms28, Oms45, and Oms66, each of about 28, 45, and 66 kDa respectively; and with average single channel conductances of about 0.6, 0.22, and 9.7 nS, respectively. Also disclosed are the methods for purifying these proteins from *B. burgdorferi*, methods for producing antibodies to these proteins, and the resulting antibodies. These proteins and their immunogenic fragments, and antibodies capable of binding to them are useful for inducing an immune response to pathogenic *B. burgdorferi* as well as providing a diagnostic target for Lyme disease. Further disclosed are the nucleotide and amino acid sequences, the cloning of the genes encoding the proteins and their recombinant proteins, and methods for obtaining the foregoing. Other *B. burgdorferi* outer membrane spanning proteins (Oms) obtainable by the isolation and purification methods of the present invention.

L7 ANSWER 45 OF 123 USPATFULL

AN 2000:156977 USPATFULL

TI \*\*\*Vaccine\*\*\* adjuvant and \*\*\*vaccine\*\*\*

IN Balasubramanian, Mannarsamy, Roswell, GA, United States

Newman, Mark Joseph, Duluth, GA, United States

Emanuele, R. Martin, Alpharetta, GA, United States

Rivera-Marrero, Carlos A., Norcross, GA, United States

Todd, Charles William, Lawrenceville, GA, United States

Brey, III, Robert Newton, Alpharetta, GA, United States

PA CytRx Corporation, DE, United States (U.S. corporation)

PI US 6149922 20001121

AI US 1998-221339 19981228 (9)

RLI Continuation of Ser. No. US 1995-513162, filed on 9 Aug 1995 which is a

continuation-in-part of Ser. No. US 1994-292814, filed on 9 Aug 1994,  
now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Salimi, Ali

LREP Jones & Askew LLP

CLMN Number of Claims: 5

ECL Exemplary Claim: 1

DRWN 52 Drawing Figure(s); 32 Drawing Page(s)

LN.CNT 1639

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention includes novel polyoxyethylene/polyoxypropylene block copolymers as well as methods for making the block copolymers. The block copolymers are high molecular weight molecules and are useful as general surfactants and display enhanced biological efficacy as \*\*\*vaccine\*\*\* adjuvants.

L7 ANSWER 46 OF 123 USPATFULL

AN 2000:153507 USPATFULL

TI Production of orthomyxoviruses in monkey kidney cells using protein-free media

IN Kistner, Otfried, Vienna, Austria

Barrett, Noel, Klosterneuburg/Weidling, Austria

Mundt, Wolfgang, Vienna, Austria

Dorner, Friedrich, Vienna, Austria

PA Baxter Aktiengesellschaft, Vienna, Austria (non-U.S. corporation)

PI US 6146873 20001114

AI US 1997-849716 19971015 (8)

RLI Continuation-in-part of Ser. No. US 1995-487046, filed on 7 Jun 1995, now patented, Pat. No. US 5753489 And a continuation-in-part of Ser. No. US 1995-487222, filed on 7 Jun 1995, now abandoned And a continuation-in-part of Ser. No. US 1995-483522, filed on 7 Jun 1995, now patented, Pat. No. US 5756341 And a continuation-in-part of Ser. No. US 1996-684729, filed on 22 Jul 1996, now patented, Pat. No. US 5698433 And a continuation-in-part of Ser. No. US 1994-338761, filed on 10 Nov 1994, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Lankford, Jr., Leon B.

LREP Foley & Lardner

CLMN Number of Claims: 37

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2487

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Viruses from the family Orthomyxoviridae, particularly influenza virus, can grow in monkey kidney cells, particularly Vero Cells, after passaging the cells in a serum-free or protein-free medium. The use of a proteolytic enzyme, especially trypsin, also aids in the propagation of the virus. The method allows for the virus to be produced to be used in a \*\*\*vaccine\*\*\*.

L7 ANSWER 47 OF 123 USPATFULL

AN 2000:153268 USPATFULL

TI \*\*\*Vaccines\*\*\*

IN Momin, Patricia Marie, Brussels, Belgium  
Garcon, Nathalie Marie-Josephe, Wavre, Belgium

PA SmithKline Beecham Biologicals s.a., Rixensart, Belgium (non-U.S.  
corporation)

PI US 6146632 20001114

WO 9517210 19950629

AI US 1996-663289 19960702 (8)

WO 1994-EP4246 19941220

19960702 PCT 371 date

19960702 PCT 102(e) date

PRAI GB 1993-26253 19931223

DT Utility

FS Granted

EXNAM Primary Examiner: Navarro, Albert

LREP Kerekes, Zoltan, Venetianer, Stephen, Kinzig, Charles M.

CLMN Number of Claims: 15

ECL Exemplary Claim: 1

DRWN 9 Drawing Figure(s); 7 Drawing Page(s)

LN.CNT 646

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides \*\*\*vaccine\*\*\* compositions comprising an oil-in-water emulsion optionally with 3 De-O-acylated monophosphoryl lipid A and QS21. The \*\*\*vaccines\*\*\* compositions are potent inducers of a range of immune responses.

L7 ANSWER 48 OF 123 USPATFULL

AN 2000:150290 USPATFULL

TI \*\*\*Borrelia\*\*\* burdorferi Osp A and B proteins and immunogenic peptides

IN Barbour, Alan George, San Antonio, TX, United States

Bergstrom, Sven, Umea, Sweden

Hansson, Lennart, Umea, Sweden

PA Symbicom Aktiebolag, S-Umea, Sweden (non-U.S. corporation)

PI US 6143872 20001107

AI US 1995-479017 19950606 (8)

RLI Continuation-in-part of Ser. No. US 1993-79601, filed on 22 Jun 1993, now patented, Pat. No. US 5523089 which is a continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now abandoned which is a continuation of Ser. No. US 1989-422881, filed on 18 Oct 1989, now abandoned 76 Ser. No. US 137175

PRAI DK 1988-5902 19881024

DT Utility

FS Granted

EXNAM Primary Examiner: Fredman, Jeffrey

LREP Frommer Lawrence & Haug LLP, Frommer, William S., Kowalski, Thomas J.

CLMN Number of Claims: 124

ECL Exemplary Claim: 1

DRWN 23 Drawing Figure(s); 22 Drawing Page(s)

LN.CNT 3789

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed and claimed are isolated polypeptides consisting of amino acid sequences derived from ospA and/or ospB of various B. burgdorferi or portions thereof and methods of making and using the same.

L7 ANSWER 49 OF 123 USPATFULL

AN 2000:138119 USPATFULL  
TI Replication defective viral vectors for infecting human cells  
IN Gruber, Harry E., San Diego, CA, United States  
Jolly, Douglas J., La Jolla, CA, United States  
Respass, James G., San Diego, CA, United States  
Laikind, Paul K., San Diego, CA, United States  
PA Chiron Corporation, Emeryville, CA, United States (U.S. corporation)  
PI US 6133029 20001017  
AI US 1995-479672 19950606 (8)  
RLI Continuation of Ser. No. US 1994-344743, filed on 23 Nov 1994, now abandoned which is a continuation of Ser. No. US 1993-139994, filed on 20 Oct 1993, now abandoned which is a continuation of Ser. No. US 1992-965084, filed on 22 Oct 1992, now abandoned which is a continuation of Ser. No. US 1990-586603, filed on 21 Sep 1990, now abandoned which is a continuation-in-part of Ser. No. US 1990-565606, filed on 10 Aug 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-395932, filed on 18 Aug 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-170515, filed on 21 Mar 1988, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Schwartzman, Robert A.

LREP Pochopien, Donald J., Blackburn, Robert P.

CLMN Number of Claims: 8

ECL Exemplary Claim: 1

DRWN 48 Drawing Figure(s); 44 Drawing Page(s)

LN.CNT 4508

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

L7 ANSWER 50 OF 123 USPATFULL

AN 2000:131635 USPATFULL

TI Recombinant swinepox virus

IN Cochran, Mark D., Carlsbad, CA, United States

Junker, David E., San Diego, CA, United States

PA Syntro Corporation, Lenexa, KS, United States (U.S. corporation)

PI US 6127163 20001003

WO 9503070 19950202

AI US 1996-295802 19960119 (8)

WO 1994-US8277 19940722

19960119 PCT 371 date

19960119 PCT 102(e) date

RLI Continuation-in-part of Ser. No. US 1992-820154, filed on 13 Jan 1992, now patented, Pat. No. US 5382425 And Ser. No. US 1993-97554, filed on

22 Jul 1993, now patented, Pat. No. US 5869312

DT Utility

FS Granted

EXNAM Primary Examiner: Mosher, Mary E.

LREP White, John P. Cooper & Dunham LLP

CLMN Number of Claims: 48

ECL Exemplary Claim: 1

DRWN 80 Drawing Figure(s); 80 Drawing Page(s)

LN.CNT 6559

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a recombinant swinepox virus capable of replication comprising foreign DNA inserted into a site in the swinepox viral DNA which is not essential for replication of the swinepox virus.

The invention further relates to homology vectors which produce recombinant swinepox viruses by inserting foreign DNA into swinepox viral DNA

L7 ANSWER 51 OF 123 USPATFULL

AN 2000:91741 USPATFULL

TI 66 kDa antigen from \*\*\*Borrelia\*\*\*

IN Bergstrom, Sven, Umea, Sweden

Barbour, Alan George, San Antonio, TX, United States

PA Symbicom AB, Umea, Sweden (non-U.S. corporation)

PI US 6090586 20000718

AI US 1995-468878 19950606 (8)

RLI Division of Ser. No. US 1994-262220, filed on 20 Jun 1994 which is a continuation-in-part of Ser. No. US 1993-79601, filed on 22 Jun 1993, now patented, Pat. No. US 5523089 which is a continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now abandoned which is a continuation of Ser. No. US 1989-422881, filed on 18 Oct 1989, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Ryan, V.

LREP Frommer, Esq., William S., Kowalski, Esq., Thomas J. Frommer Lawrence & Haug LLP

CLMN Number of Claims: 21

ECL Exemplary Claim: 1

DRWN 11 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 3064

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to nucleic acid molecules, polypeptides encoded by the same, antibodies directed thereto and a method of preparing such polypeptides including: (a) inserting an isolated DNA molecule coding for a polypeptide which is immunoreactive with a 66 kDa polypeptide derived from \*\*\*Borrelia\*\*\* garinii IP90 into an expression vector; (b) transforming a host organism or cell with the vector; (c) culturing the transformed host cell under suitable conditions; and (d) harvesting the polypeptide. The isolated DNA molecule is preferably at least 10 nucleotides in length, and the method may optionally include subjecting the polypeptide to post-translational modification. The host cell can be a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism such as a fungus, an insect cell, a plant cell, or a mammalian cell.

L7 ANSWER 52 OF 123 USPATFULL

AN 2000:91548 USPATFULL  
TI Recombinant canine adenoviruses, method for making and uses thereof  
IN Fischer, Laurent, Albany, NY, United States  
PA Merial, Lyons, France (non-U.S. corporation)  
PI US 6090393 20000718  
AI US 1996-675566 19960703 (8)  
DT Utility  
FS Granted

EXNAM Primary Examiner: Stucker, Jeffrey  
LREP Frommer, Lawrence & Haug LLP, Frommer, William S., Kowalski, Thomas J.  
CLMN Number of Claims: 23  
ECL Exemplary Claim: 1  
DRWN 50 Drawing Figure(s); 97 Drawing Page(s)  
LN.CNT 7094

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed and claimed are recombinant adenoviruses, methods of making them, uses for them (including in immunological, immunogenic, \*\*\*vaccine\*\*\* or therapeutic compositions, or, as a vector for cloning, replicating or expressing DNA and methods of using the compositions and vector), expression products from them, and uses for the expression products. More particularly, disclosed and claimed are recombinant canine adenoviruses (CAV) and methods of making them, uses for them, expression products from them, and uses for the expression products, including recombinant CAV2 viruses. Additionally, disclosed and claimed are truncated promoters, expression cassettes containing the promoters, and recombinant viruses and plasmids containing the promoters or expression cassettes.

L7 ANSWER 53 OF 123 USPATFULL  
AN 2000:87730 USPATFULL  
TI \*\*\*Vaccine\*\*\* adjuvant and \*\*\*vaccine\*\*\*  
IN Balasubramanian, Mannarsamy, Roswell, GA, United States  
Newman, Mark Joseph, Duluth, GA, United States  
Emanuele, R. Martin, Alpharetta, GA, United States  
Rivera-Marrero, Carlos A., Norcross, GA, United States  
Todd, Charles William, Lawrenceville, GA, United States  
Brey, III, Robert Newton, Alpharetta, GA, United States  
PA CytRx Corporation, Norcross, GA, United States (U.S. corporation)  
PI US 6086899 20000711  
AI US 1995-513162 19950809 (8)

RLI Continuation-in-part of Ser. No. US 1994-292814, filed on 9 Aug 1994,  
now abandoned

DT Utility  
FS Granted

EXNAM Primary Examiner: Mosher, Mary E.; Assistant Examiner: Salimi, Ali R

LREP Jones & Askew, LLP

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN 32 Drawing Figure(s); 32 Drawing Page(s)

LN.CNT 1679

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention includes novel polyoxyethylene/polyoxypropylene block copolymers as well as methods for making the block copolymers. The block copolymers are high molecular weight molecules and are useful as general surfactants and display enhanced biological efficacy as

\*\*\*vaccine\*\*\* adjuvants.

L7 ANSWER 54 OF 123 USPATFULL  
AN 2000:87712 USPATFULL  
TI Spatially aligned conjugated composition having a thioether bond linkage  
IN Frey, Andreas, Muenster, Germany, Federal Republic of  
Neutra, Marian R., Sherborn, MA, United States  
Robey, Frank A., Bethesda, MD, United States  
PA Children's Medical Center Corp., Boston, MA, United States (U.S.  
corporation)  
PI US 6086881 20000711  
AI US 1998-79374 19980515 (9)  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Park, Hankyel  
LREP Prashker, David  
CLMN Number of Claims: 11  
ECL Exemplary Claim: 1  
DRWN 9 Drawing Figure(s); 8 Drawing Page(s)  
LN.CNT 1674  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is a spatially aligned conjugated composition which comprises at least one chemically modified substance which is immunologically representative of a prechosen infectious agent and provides a chemical constituent for entering into and forming a thioether bond; a plurality of chemically substituted metallic oxide particles which range from about 10-10,000 nanometers and are able to enter into a thioether bond and covalent linkage; and at least one thioether bond and linkage joining the metallic oxide particles in a controlled and spatially aligned manner to the antigen or hapten. The conjugated composition may be alternatively employed as an immunogen; as a \*\*\*vaccine\*\*\* ; as a diagnostic tool and reactant; and as an analytical material suitable for testing the pharmacological activity of new compounds.

L7 ANSWER 55 OF 123 USPATFULL  
AN 2000:84063 USPATFULL  
TI \*\*\*Borrelia\*\*\* antigen  
IN Bergstrom, Sven, Umea, Sweden  
Barbour, Alan G., San Antonio, TX, United States  
Magnarelli, Louis A., Durham, CT, United States  
PA Symbicom AB, Ume.ang., Sweden (non-U.S. corporation)  
PI US 6083722 20000704  
AI US 1995-471019 19950606 (8)  
RLI Division of Ser. No. US 1995-375993, filed on 20 Jan 1995, now patented,  
Pat. No. US 5688512 which is a division of Ser. No. US 1993-79601, filed  
on 22 Jun 1993, now patented, Pat. No. US 5523089 which is a  
continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now  
abandoned which is a continuation of Ser. No. US 1989-442881, filed on  
18 Oct 1989, now abandoned  
PRAI DK 1988-5902 19881024  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Swartz, Rodney  
P.

LREP Frommer Lawrence & Haug LLP, Frommer, William S., Kowalski, Thomas J.  
CLMN Number of Claims: 30

ECL Exemplary Claim: 1

DRWN 24 Drawing Figure(s); 24 Drawing Page(s)

LN.CNT 2716

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed and claimed are Lyme disease \*\*\*vaccines\*\*\* and methods for making and using them. The \*\*\*vaccines\*\*\* include a vector containing DNA encoding OspA or an immunogenic fragment thereof or such DNA encoding OspA or an immunogenic fragment thereof which has been modified by substitution, addition, insertion or deletion of one or more nucleotides, whereby the DNA when expressed results in OspA, or an immunogenic fragment thereof, or a polypeptide having the immunological activity of OspA or the fragment thereof.

L7 ANSWER 56 OF 123 USPATFULL

AN 2000:67433 USPATFULL

TI 66 kDa antigen from \*\*\*Borrelia\*\*\*

IN Bergstrom, Sven, Umea, Sweden

Barbour, Alan George, San Antonio, TX, United States

PA Symbicom AB, Ulmea, Sweden (non-U.S. corporation)

PI US 6068842 20000530

AI US 1995-471733 19950606 (8)

RLI Division of Ser. No. US 1994-262220, filed on 20 Jun 1994 which is a continuation-in-part of Ser. No. US 1993-79601, filed on 22 Jun 1993, now patented, Pat. No. US 5523089 which is a continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now abandoned which is a continuation of Ser. No. US 1989-422881, filed on 18 Oct 1989, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Ryan, V.

LREP Frommer, Esq., William S., Kowalski, Esq., Thomas J. Frommer Lawerence & Haug LLP

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN 11 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 3138

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to nucleic acid molecules, polypeptides encoded by the same, antibodies directed thereto and a method of preparing such polypeptides including: (a) inserting an isolated DNA molecule coding for a polypeptide which is immunoreactive with a 66 kDa polypeptide derived from \*\*\*Borrelia\*\*\* garinii IP90 into an expression vector; (b) transforming a host organism or cell with the vector; (c) culturing the transformed host cell under suitable conditions; and (d) harvesting the polypeptide. The isolated DNA molecule is preferably at least 10 nucleotides in length, and the method may optionally include subjecting the polypeptide to post-translational modification. The host cell can be a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism such as a fungus, an insect cell, a plant cell, or a mammalian cell.

L7 ANSWER 57 OF 123 USPATFULL

AN 2000:57554 USPATFULL

TI Mycobacterium proteins and applications

IN Marchal, Gilles, Ivry, France  
Romain, Felix, Fontenay-Les-Briis, France  
Pescher, Pascale, Paris, France  
Horn, Cynthia, Paris, France  
PA Institut Pasteur, Paris Cedex, France (non-U.S. corporation)  
PI US 6060259 20000509  
AI US 1994-351134 19941130 (8)  
RLI Continuation-in-part of Ser. No. WO 1992-FR508, filed on 5 Jun 1992  
PRAI FR 1991-6970 19910607  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Graser, Jennifer  
LREP Oblon, Spivak, McClelland, Maier & Neustadt, P.C.  
CLMN Number of Claims: 11  
ECL Exemplary Claim: 1  
DRWN 13 Drawing Figure(s); 11 Drawing Page(s)  
LN.CNT 919

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Mycobacterium proteins, in particular those of *M. bovis*, having molecular weights between approximately 44.5 and 47.5 kD. These proteins can have molecular weights of approximately 45 kD or 47 kD and isoelectric pH of approximately 3.7 (45 and 47 kD proteins) and 3.9 (47 kD proteins).

These proteins or hybrid proteins containing a part of their sequences can be used as \*\*\*vaccines\*\*\* or as drugs, or for the detection and monitoring of tuberculosis in particular in man and in cattle.

L7 ANSWER 58 OF 123 USPATFULL  
AN 2000:50546 USPATFULL  
TI 66 kDa antigen from \*\*\**Borrelia*\*\*\*  
IN Bergstrom, Sven, Umea, Sweden  
Barbour, Alan George, San Antonio, TX, United States  
PA Symbicom AB, Umea, Sweden (non-U.S. corporation)  
PI US 6054296 20000425  
AI US 1994-262220 19940620 (8)  
RLI Continuation-in-part of Ser. No. US 1993-79601, filed on 22 Jun 1993, now patented, Pat. No. US 5523089 which is a continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now abandoned which is a continuation of Ser. No. US 1989-422881, filed on 18 Oct 1989, now abandoned

PRAI DK 1988-5902 19881024

DT Utility  
FS Granted

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Ryan, V.  
LREP Frommer, Esq., William S., Kowalski, Esq., Thomas J. Frommer Lawrence & Haug LLP

CLMN Number of Claims: 32

ECL Exemplary Claim: 1  
DRWN 11 Drawing Figure(s); 5 Drawing Page(s)  
LN.CNT 3433

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to nucleic acid molecules, polypeptides encoded by the same, antibodies directed thereto and a method of preparing such polypeptides including: (a) inserting an isolated DNA molecule coding for a polypeptide which is immunoreactive with a 66 kDa

polypeptide derived from \*\*\*Borrelia\*\*\* garinii IP90 into an expression vector; (b) transforming a host organism or cell with the vector; (c) culturing the transformed host cell under suitable conditions; and (d) harvesting the polypeptide. The isolated DNA molecule is preferably at least 10 nucleotides in length, and the method may optionally include subjecting the polypeptide to post-translational modification. The host cell can be a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism such as a fungus, an insect cell, a plant cell, or a mammalian cell.

L7 ANSWER 59 OF 123 USPATFULL

AN 2000:37383 USPATFULL

TI Parasitic helminth asparaginase proteins, nucleic acid molecules, and uses thereof

IN Chandrashekhar, Ramaswamy, Fort Collins, CO, United States  
Tsui, Naotsoshi, Fort Collins, CO, United States

PA Heska Corporation, Fort Collins, CO, United States (U.S. corporation)  
Colorado State University Research Foundation, Fort Collins, CO, United States (U.S. corporation)

PI US 6042825 20000328

AI US 1998-140177 19980825 (9)

RLI Division of Ser. No. US 1997-929501, filed on 15 Sep 1997, now patented,  
Pat. No. US 5854051

DT Utility

FS Granted

EXNAM Primary Examiner: Nashed, Nashaat T.

LREP Heska Corporation

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2863

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to: parasitic helminth asparaginase proteins; parasitic helminth asparaginase nucleic acid molecules, including those that encode such asparaginase proteins; antibodies raised against such asparaginase proteins; and compounds that inhibit parasitic helminth asparaginase activity. The present invention also includes methods to obtain such proteins, nucleic acid molecules, antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to protect animals from diseases caused by parasitic helminths.

L7 ANSWER 60 OF 123 USPATFULL

AN 2000:27800 USPATFULL

TI Recombinant swinepox virus

IN Cochran, Mark D., Carlsbad, CA, United States  
Junker, David E., San Diego, CA, United States

PA Syntro Corporation, Lenexa, KS, United States (U.S. corporation)

PI US 6033904 20000307

AI US 1995-480640 19950607 (8)

RLI Continuation-in-part of Ser. No. US 1995-375922, filed on 19 Jan 1995  
which is a continuation-in-part of Ser. No. WO 1994-US8277, filed on 22 Jul 1994 which is a continuation-in-part of Ser. No. US 1993-97554,

filed on 22 Jul 1993, now patented, Pat. No. US 5869312 And a continuation-in-part of Ser. No. US 1992-820154, filed on 13 Jan 1992, now patented, Pat. No. US 5382425, issued on 17 Jan 1995

DT Utility

FS Granted

EXNAM Primary Examiner: Mosher, Mary E.; Assistant Examiner: Salini, Ali R  
LREP White, John P. Copper & Dunham LLP

CLMN Number of Claims: 32

ECL Exemplary Claim: 1,7

DRWN 114 Drawing Figure(s); 114 Drawing Page(s)

LN.CNT 8999

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a recombinant swinepox virus comprising a foreign DNA sequence inserted into the swinepox virus genomic DNA, wherein the foreign DNA sequence is inserted within a HindIII N fragment of the swinepox virus genomic DNA and is capable of being expressed in a swinepox virus infected host cell. The invention further provides homology vectors, \*\*\*vaccines\*\*\* and methods of immunization.

L7 ANSWER 61 OF 123 USPATFULL

AN 2000:27752 USPATFULL

TI Promoter of the cdc25B gene, its preparation and use

IN Koerner, Kathrin, Marburg, Germany, Federal Republic of  
Mueller, Rolf, Marburg, Germany, Federal Republic of

Sedlacek, Hans-Harald, Marburg, Germany, Federal Republic of

PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic  
of (non-U.S. corporation)

PI US 6033856 20000307

AI US 1998-39555 19980316 (9)

PRAI DE 1997-19710643 19970314

DT Utility

FS Granted

EXNAM Primary Examiner: Schwartzman, Robert A.

LREP Foley & Lardner

CLMN Number of Claims: 43

ECL Exemplary Claim: 42

DRWN 10 Drawing Figure(s); 8 Drawing Page(s)

LN.CNT 2848

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides the promoter of the cdc25B gene, a process for finding cdc25B promoters and methods for using the promoters for preparing a pharmaceutical.

L7 ANSWER 62 OF 123 USPATFULL

AN 2000:9723 USPATFULL

TI Unique nucleotide and amino acid sequence and uses thereof

IN Summers, Max D., Bryan, TX, United States

Braunagel, Sharon C., Bryan, TX, United States

Hong, Tao, Bryan, TX, United States

PA The Texas A & M University System, College Station, TX, United States  
(U.S. corporation)

PI US 6017734 20000125

AI US 1997-792832 19970130 (8)

RLI Continuation-in-part of Ser. No. US 1996-678435, filed on 3 Jul 1996,  
now abandoned

PRAI US 1995-955 19950707 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman,  
Robert

LREP Arnold, White & Durkee

CLMN Number of Claims: 56

ECL Exemplary Claim: 1

DRWN 47 Drawing Figure(s); 24 Drawing Page(s)

LN.CNT 7846

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided are hydrophobic targeting sequences, which may serve to target heterologous proteins to a variety of cellular membranes. In particular, the structural components of the nuclear envelope, or those components which become nucleus-associated, may be targeted with the sequences provided. Also provided are methods of targeting heterologous proteins to particular membranes, and the use of these targeted proteins in therapeutic, diagnostic and insecticidal applications.

L7 ANSWER 63 OF 123 CABO COPYRIGHT 2002 CABI DUPLICATE 2

AN 2001:108153 CABO

DN 20013105483

TI Characterization of a \*\*\*Borrelia\*\*\* burgdorferi VlsE invariable region useful in canine Lyme disease serodiagnosis by enzyme-linked immunosorbent assay

AU Liang FangTing; Jacobson, R. H.; Straubinger, R. K.; Grooters, A.; Philipp, M. T.; Liang, F. T.

CS Department of Parasitology, Tulane Regional Primate Research Center, Tulane University Health Sciences Center, 18703 Three Rivers Rd., Covington, LA 70433, USA.

SO Journal of Clinical Microbiology, (2000) Vol. 38, No. 11, pp. 4160-4166.

23 ref.

ISSN: 0095-1137

DT Journal

LA English

AB Sera collected from dogs experimentally infected with \*\*\*Borrelia\*\*\* burgdorferi by tick inoculation were analysed for an antibody response to each of the 6 invariable regions (IRs; i.e., IR1 to IR6) of VlsE, the variable \*\*\*surface\*\*\* \*\*\*antigen\*\*\* of *B. burgdorferi*. Six synthetic peptides (C1 to C6), which reproduced the six IR sequences were used as peptide-based, ELISA antigens. Two IRs, IR2 and IR6, were found to be immunodominant. Studies with serially collected serum samples from experimentally infected dogs revealed that the antibody response to IR6 appears earlier and is stronger than that to IR2. Thus, the IR6 sequence alone appeared to be sufficient for serodiagnosis. When C6 alone was used as antigen, the peptide-based ELISA was positive in 7 of 23 dogs (30%) as early as 3 weeks postinfection. All dogs (n = 33) became strongly positive 1 or 2 weeks later, and this response persisted for the entire study, which lasted for 69 weeks. Of 55 sera submitted by veterinarians from dogs suspected of having Lyme disease, 19 were also positive by the C6 ELISA, compared to 20 positives detected by immunoblot analysis using cultured *B. burgdorferi* lysates as antigen. The sensitivity of using C2 and C6 together for detecting specific antibody in both experimentally infected and clinically diagnosed dogs was not better than sensitivity with C6 alone, confirming that C6 suffices as a diagnostic probe. Moreover, the C6

ELISA yielded 100% specificity with serum samples collected from 70 healthy dogs, 14 dogs with infections other than *B. burgdorferi*, and 15 animals vaccinated with either outer surface protein A, whole-spirochaete \*\*\*vaccines\*\*\*, or the common puppy- \*\*\*vaccines\*\*\*. Therefore, this C6 ELISA was both sensitive and specific for the serodiagnosis of canine Lyme disease and could be used with vaccinated dogs.

L7 ANSWER 64 OF 123 SCISEARCH COPYRIGHT 2002 ISI (R)  
AN 2000:413842 SCISEARCH  
GA The Genuine Article (R) Number: 318WM  
TI Cryptic and exposed invariable regions of VlsE, the variable \*\*\*surface\*\*\* \*\*\*antigen\*\*\* of \*\*\**Borrelia*\*\*\* *burgdorferi* sl  
AU Liang F T; Nowling J M; Philipp M T (Reprint)  
CS TULANE UNIV, MED CTR, TULANE REG PRIMATE RES CTR, DEPT PARASITOL, 18703 3 RIVERS RD, COVINGTON, LA 70433 (Reprint); TULANE UNIV, MED CTR, TULANE REG PRIMATE RES CTR, DEPT PARASITOL, COVINGTON, LA 70433  
CYA USA  
SO JOURNAL OF BACTERIOLOGY, (JUN 2000) Vol. 182, No. 12, pp. 3597-3601.  
Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904.  
ISSN: 0021-9193.  
DT Article; Journal  
FS LIFE  
LA English  
REC Reference Count: 23  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
AB \*\*\**Borrelia*\*\*\* *burgdorferi*, the Lyme disease spirochete, possesses a surface protein, VlsE, which undergoes antigenic variation. VlsE contains two invariable domains and a variable one that includes six variable and six invariable regions (IRs). Five of the IRs are conserved among strains and genospecies of *B. burgdorferi* sensu lato. IR<sub>1</sub> is conserved, immunodominant, and exposed at the VlsE surface but not at the spirochete surface, as assessed in vitro. In the present study, the remaining conserved IRs (IR<sub>2</sub> to IR<sub>5</sub>) were investigated. Antisera to synthetic peptides based on each of the IR<sub>1</sub> to IR<sub>5</sub> sequences were produced in rabbits. Antipeptide antibody titers were similarly high in all antisera. Native VlsE was immunoprecipitable with antibodies to IR<sub>2</sub>, IR<sub>4</sub>, and IR<sub>5</sub> but not to IR<sub>3</sub>, indicating that the first three sequences were exposed at the VlsE surface. However, negative surface immunofluorescence and in vitro antibody-mediated killing results indicated that none of the IRs were accessible to antibody at the spirochetal surface in vitro.

L7 ANSWER 65 OF 123 SCISEARCH COPYRIGHT 2002 ISI (R)  
AN 2000:372513 SCISEARCH  
GA The Genuine Article (R) Number: 313BN  
TI Efficient vaccination by intradermal or intramuscular inoculation of plasmid DNA expressing hepatitis B \*\*\*surface\*\*\* \*\*\*antigen\*\*\* under desmin promoter/enhancer control  
AU Kwissa M; vonKampen J; Zurbriggen R; Gluck R; Reimann J (Reprint); Schirmbeck R  
CS UNIV ULM, INST MED MICROBIOL, HELMHOLTZSTR 8-1, D-89081 ULM, GERMANY (Reprint); UNIV ULM, INST MED MICROBIOL, D-89081 ULM, GERMANY; SWISS SERUM & VACCINE INST, BERNA, BERN, SWITZERLAND  
CYA GERMANY; SWITZERLAND  
SO VACCINE, (8 MAY 2000) Vol. 18, No. 22, pp. 2337-2344.  
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON,

OXFORD OX5 1GB, OXON, ENGLAND.

ISSN: 0264-410X.

DT Article; Journal

FS LIFE; AGRI

LA English

REC Reference Count: 26

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The small \*\*\*surface\*\*\* \*\*\*antigen\*\*\* of the hepatitis B virus (HBsAg) was cloned into expression plasmid pCI under either a viral (CMV) promoter/enhancer sequence control (plasmid pCI/S), or a human desmin promoter/enhancer sequence control (plasmid pDes/S). Cells of different species and tissue origin transiently transfected in vitro with pCI/S or pDes/S plasmid DNA expressed readily detectable amounts of HBsAg, either intracellularly (precipitated from cell lysates), or as secreted products (detectable in ELISA). When these plasmids were used in DNA vaccination, both efficiently primed humoral and/or cellular immune responses to HBsAg after a single injection in Balb/c mice. Intramuscular injection of a high dose of DNA (100 mu g/mouse) of both plasmids primed MHC-I-restricted cytotoxic T lymphocyte (CTL) responses and Th1 serum antibody responses (IgG1/IgG2a ratio 0.4-0.7) of comparable magnitude in all vaccinated mice. Intradermal injection of low doses of (particle-coated) DNA (1 mu g/mouse) of both plasmids with the gene gun primed Th2 serum antibody responses (IgG1/IgG2a ratio > 100) but no CTL responses. The data indicate that antigens can be efficiently expressed under viral or eukaryotic promoter/enhancer control for immunogenic in vivo presentation, but that the technique, dose and/or route of DNA injection have a decisive role in determining the type of immune response elicited. (C) 2000 Elsevier Science Ltd. All rights reserved.

L7 ANSWER 66 OF 123 CAPLUS COPYRIGHT 2002 ACS

AN 1999:194170 CAPLUS

DN 130:236453

TI P13 antigens and P13 genes of Lyme disease \*\*\*Borrelia\*\*\* and methods for diagnosis and vaccination

IN Bergstrom, Sven

PA Symbicom Ab, Swed.

SO PCT Int. Appl., 118 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9912960	A2	19990318	WO 1998-IB1424	19980904
WO 9912960	A3	19990527		
W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9888811	A1	19990329	AU 1998-88811	19980904

EP 1012269 A2 20000628 EP 1998-940504 19980904  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, FI  
PRAI DK 1997-1041 A 19970910  
US 1997-59036 P 19970916  
WO 1998-IB1424 W 19980904  
AB A 13 kDa cell \*\*\*surface\*\*\* \*\*\*antigen\*\*\* (P13) found on Lyme disease \*\*\*Borrelia\*\*\* (B. burgdorferi, B. garinii, B. afzelii) but not B. hermsii, B. crocidurae, B. anserina, or B. hispanica and the gene for P13 are disclosed. Addnl. P13 epitopes, vectors, transformed cells, a method of prep. P13 or P13 epitopes, and \*\*\*vaccines\*\*\* as well as diagnostic compns. and kits are further disclosed. The P13 genes of the 3 Lyme disease \*\*\*Borrelia\*\*\* were cloned and sequenced. The B. burgdorferi P13 gene was expressed in Escherichia coli.

L7 ANSWER 67 OF 123 CAPLUS COPYRIGHT 2002 ACS

AN 1999:34932 CAPLUS

DN 130:109201

TI \*\*\*Surface\*\*\* \*\*\*antigens\*\*\* and proteins useful in compositions for the diagnosis and prevention of Lyme disease

IN Philipp, Mario T.

PA The Administrators of the Tulane Educational Fund, USA

SO PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

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PI WO 9900413 A1 19990107 WO 1998-US13551 19980629  
W: AU, BR, CA, CN, CZ, HU, ID, IL, JP, KR, MX, NO, NZ, PL, TR, US  
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE  
AU 9881772 A1 19990119 AU 1998-81772 19980629  
EP 1012181 A1 20000628 EP 1998-931729 19980629  
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, FI  
ZA 9805704 A 19990113 ZA 1998-5704 19980630  
NO 9906514 A 20000214 NO 1999-6514 19991228

PRAI US 1997-51271 P 19970630

WO 1998-US13551 W 19980629

AB A novel isolated \*\*\*Borrelia\*\*\* burgdorferi sensu lato \*\*\*surface\*\*\* \*\*\*antigen\*\*\* is characterized by a relative mol. mass of 39.5 kDa. This antigen is expressed in vitro by spirochetes of a B. burgdorferi sensu lato strain. This antigen induces antibodies which kill spirochetes of a B. burgdorferi sensu lato strain by ADCK in vitro. Novel \*\*\*Borrelia\*\*\* cassette string protein or fragments thereof are also useful, as is the P39.5 protein in diagnosing Lyme disease and in compns. for treatment or prophylaxis thereof.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 68 OF 123 USPATFULL

AN 1999:159476 USPATFULL

TI Method for treating a metastatic carcinoma using a conditionally lethal gene

IN Barber, Jack R., San Diego, CA, United States  
Gruber, Harry E., San Diego, CA, United States  
Jolly, Douglas J., Leucadia, CA, United States  
PA Chiron Corporation, Emeryville, CA, United States (U.S. corporation)  
PI US 5997859 19991207  
AI US 1995-467034 19950606 (8)  
RLI Division of Ser. No. US 1993-155944, filed on 18 Nov 1993, now abandoned  
which is a continuation-in-part of Ser. No. US 1993-139994, filed on 20  
Oct 1993, now abandoned which is a continuation of Ser. No. US  
1992-965084, filed on 22 Oct 1992, now abandoned which is a continuation  
of Ser. No. US 1990-586603, filed on 21 Sep 1990, now abandoned which is  
a continuation-in-part of Ser. No. US 1990-565606, filed on 10 Aug 1990,  
now abandoned which is a continuation-in-part of Ser. No. US  
1989-395932, filed on 18 Aug 1989, now abandoned which is a  
continuation-in-part of Ser. No. US 1988-170515, filed on 21 Mar 1988,  
now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman,  
Robert

LREP Pochopien, Donald J., Blackburn, Robert P.

CLMN Number of Claims: 19

ECL Exemplary Claim: 1

DRWN 30 Drawing Figure(s); 25 Drawing Page(s)

LN.CNT 2772

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides recombinant viral vectors carrying a  
vector construct which directs the expression of a gene product (e.g.,  
HSVTK) that activates a compound with little or no cytotoxicity into a  
toxic product. Also provided are methods of destroying or inhibiting  
pathogenic agents in a warm blooded animal, comprising the step of  
administering to the animal a viral vector such as that described above,  
in order to inhibit or destroy the pathogenic agent.

L7 ANSWER 69 OF 123 USPATFULL

AN 1999:150655 USPATFULL

TI Antigen carbohydrate compounds and their use in immunotherapy

IN McKenzie, Ian F. C., Victoria, Australia

Pietersz, Geoff Allen, Victoria, Australia

Apostolopoulos, Vasso, Victoria, Australia

PA Austin Research Institute, Victoria, Australia (non-U.S. corporation)

PI US 5989552 19991123

AI US 1997-833807 19970409 (8)

RLI Continuation of Ser. No. US 1994-340711, filed on 16 Nov 1994, now  
abandoned

PRAI AU 1993-3223 19931224

DT Utility

FS Granted

EXNAM Primary Examiner: Knodel, Marian C.; Assistant Examiner: Williams, Jay F.

LREP Dann, Dorfman, Herrell And Skillman

CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN 11 Drawing Figure(s); 10 Drawing Page(s)

LN.CNT 1551

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Conjugates between one or more repeated subunits of an antigen and a carbohydrate polymer are desired. Also described are immunogenic \*\*\*vaccines\*\*\* against disease states which contain the conjugates and methods for inducing cell-mediated immune responses. The conjugates may especially contain polymers of the carbohydrate mannose and one or more repeated subunits of human mucin.

L7 ANSWER 70 OF 123 USPATFULL

AN 1999:141912 USPATFULL

TI Compositions and methods for delivery of genetic material

IN Weiner, David B., Merion, PA, United States

Williams, William V., Havertown, PA, United States

Wang, Bin, Havertown, PA, United States

PA The Trustees of The University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)

The Wistar Institute, Philadelphia, PA, United States (U.S. corporation)

PI US 5981505 19991109

WO 9416737 19940804

AI US 1997-979385 19971126 (8)

WO 1994-US899 19940126

19950828 PCT 371 date

19950828 PCT 102(e) date

RLI Continuation-in-part of Ser. No. US 1993-124962, filed on 21 Sep 1993, now abandoned And a continuation-in-part of Ser. No. US 1993-93235, filed on 15 Jul 1993, now abandoned And a continuation of Ser. No. US 1995-495684, filed on 28 Aug 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-125012, filed on 21 Sep 1993, now patented, Pat. No. US 5593972, issued on 14 Jan 1997 which is a continuation-in-part of Ser. No. US 1993-29336, filed on 11 Mar 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-8342, filed on 26 Jan 1993, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Railey, II, Johnny F.

LREP Woodcock Washburn Kurtz Mackiewicz & Norris LLP

CLMN Number of Claims: 75

ECL Exemplary Claim: 1

DRWN 23 Drawing Figure(s); 12 Drawing Page(s)

LN.CNT 4084

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of inducing genetic material into cells of an individual and compositions and kits for practicing the same are disclosed. The methods comprise the steps of contacting cells of an individual with a polynucleotide function enhancer and administering to the cells, a nucleic acid molecule that is free of retroviral particles. The nucleic acid molecule comprises a nucleotide sequence that encodes a protein that comprises at least one epitope that is identical or substantially similar to an epitope of a pathogen antigen or an antigen associated with a hyperproliferative or autoimmune disease, a protein otherwise missing from the individual due to a missing, non-functional or partially functioning gene, or a protein that produces a therapeutic effect on an individual. Methods of prophylactically and therapeutically immunizing an individual against HIV are disclosed. Pharmaceutical compositions and kits for practicing methods of the present invention are disclosed.

L7 ANSWER 71 OF 123 USPATFULL  
AN 1999:124475 USPATFULL  
TI Recombinant chimeric virus and uses thereof  
IN Cochran, Mark D., Carlsbad, CA, United States  
Junker, David E., San Diego, CA, United States  
Wild, Martha A., San Diego, CA, United States  
Singer, Phillip A., San Diego, CA, United States  
PA Syntro Corporation, Lenexa, KS, United States (U.S. corporation)  
PI US 5965138 19991012  
AI US 1994-362240 19941222 (8)  
RLI Continuation of Ser. No. US 1994-288065, filed on 9 Aug 1994 And a continuation-in-part of Ser. No. WO 1993-US5681, filed on 14 Jun 1993 Ser. No. Ser. No. US 1992-898087, filed on 12 Jun 1992, now abandoned Ser. No. Ser. No. US 1988-225032, filed on 21 Jul 1988, now patented, Pat. No. US 5223424, issued on 29 Jun 1993 Ser. No. Ser. No. US 1991-649380, filed on 31 Jan 1991, now abandoned And Ser. No. US 1992-914057, filed on 13 Jul 1992, now abandoned which is a continuation of Ser. No. US 1991-696262, filed on 30 Apr 1991, now abandoned which is a continuation of Ser. No. US 1986-933107, filed on 20 Nov 1986, now abandoned which is a continuation-in-part of Ser. No. US 1985-773430, filed on 6 Sep 1985, now patented, Pat. No. US 4877737, issued on 31 Oct 1989 And Ser. No. US 1986-823102, filed on 27 Jan 1986, now patented, Pat. No. US 5068192 , said Ser. No. US 288065 which is a continuation of Ser. No. US 1993-23610, filed on 26 Feb 1993 , said Ser. No. US 225032 which is a continuation-in-part of Ser. No. US 1987-78519, filed on 27 Jul 1987, now abandoned Ser. No. Ser. No. US 1986-933107, filed on 20 Nov 1986, now abandoned Ser. No. Ser. No. US 1986-902887, filed on 2 Sep 1986, now abandoned Ser. No. Ser. No. US 1986-823102, filed on 27 Jan 1986, now patented, Pat. No. US 5068192, issued on 26 Nov 1991 And Ser. No. US 1985-773430, filed on 6 Sep 1985, now patented, Pat. No. US 4877737, issued on 31 Oct 1989 , said Ser. No. US 649380 which is a continuation of Ser. No. US 78519 which is a continuation-in-part of Ser. No. US 993107 Ser. No. Ser. No. US 902877 Ser. No. Ser. No. US 1986-887140, filed on 17 Jul 1986, now abandoned Ser. No. Ser. No. US 823102 And Ser. No. US 773430

DT Utility

FS Granted

EXNAM Primary Examiner: Knodel, Marian C.; Assistant Examiner: Salimi, Ali R.

LREP White, John P. Cooper & Dunham LLP

CLMN Number of Claims: 21

ECL Exemplary Claim: 1

DRWN 28 Drawing Figure(s); 25 Drawing Page(s)

LN.CNT 6177

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a recombinant herpesvirus of turkeys comprising a herpesvirus of turkeys viral genome which contains a foreign DNA sequence inserted within the EcoR1 #9 fragment of the herpesvirus of turkeys viral genome, and the foreign DNA sequence is capable of being expressed in a host cell infected with the herpesvirus of turkeys.

This invention provides a recombinant herpesvirus of turkeys-Marek's disease virus chimera comprising a herpesvirus of turkeys unique long viral genome region and a Marek's disease virus unique short region.

Lastly, this invention provides homology vectors for producing a recombinant herpesvirus of turkeys, host cells, and \*\*\*vaccines\*\*\* and methods for immunization.

L7 ANSWER 72 OF 123 USPATFULL

AN 1999:121330 USPATFULL

TI Compositions and methods for delivery of genetic material

IN Carrano, Richard A., Paoli, PA, United States

Wang, Bin, Haidian, China

Weiner, David B., Merion, PA, United States

PA Apollon, Inc., Malvern, PA, United States (U.S. corporation)

The Trustees Of The University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)

PI US 5962428 19991005

WO 9526718 19951012

AI US 1996-704701 19960916 (8)

WO 1995-US4071 19950330

19960916 PCT 371 date

19960916 PCT 102(e) date

RLI Continuation of Ser. No. US 221579

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman, Robert

LREP Woodcock Washburn Kurtz Mackiewcz & Norris LLP

CLMN Number of Claims: 42

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 3606

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of introducing genetic material into cells of an individual and compositions and kits for practicing the same are disclosed. The methods comprise the steps of contacting cells of an individual with a genetic \*\*\*vaccine\*\*\* facilitator and administering to the cells a nucleic acid molecule that is free of retroviral particles. The nucleic acid molecule comprises a nucleotide sequence that encodes a protein that comprises at least one epitope that is identical or substantially similar to an epitope of a pathogen antigen or an antigen associated with a hyperproliferative or autoimmune disease, a protein otherwise missing from the individual due to a missing, non-functional or partially functioning gene, or a protein that produces a therapeutic effect on an individual. Methods of prophylactically and therapeutically immunizing an individual against HIV are disclosed. Pharmaceutical compositions and kits for practicing methods of the present invention are disclosed.

L7 ANSWER 73 OF 123 USPATFULL

AN 1999:121143 USPATFULL

TI Mycobacterium proteins and applications

IN Marchal, Gilles, Ivry, France

Romain, Felix, Fontenay-les-Briis, France

Pescher, Pascale, Paris, France

PA Institut Pasteur, Paris Cedex, France (non-U.S. corporation)

PI US 5962240 19991005

WO 9221758 19921210

AI US 1995-142483 19950503 (8)  
WO 1992-FR508 19920605  
19950503 PCT 371 date  
19950503 PCT 102(e) date

PRAI FR 1991-6970 19910607

DT Utility

FS Granted

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Graser, Jennifer  
LREP Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 9 Drawing Figure(s); 8 Drawing Page(s)

LN.CNT 733

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Mycobacterium proteins, in particular those of *M. bovis*, having molecular weights between approximately 44.5 and 47.5 kD. These proteins can have molecular weights of approximately 45 kD or 47 kD and isoelectric pH of approximately 3.7 (45 and 47 kD proteins) and 3.9 (47 kD proteins).

These proteins or hybrid proteins containing a part of their sequences can be used as \*\*\*vaccines\*\*\* or as drugs, or for the detection and monitoring of tuberculosis in particular in man and in cattle.

L7 ANSWER 74 OF 123 USPATFULL

AN 1999:88799 USPATFULL

TI Diagnostic tests for a new spirochete, \*\*\**Borrelia*\*\*\* *lonestari* sp.  
nov.

IN Barbour, Alan G., San Antonio, TX, United States  
Carter, Carol, Bulverde, TX, United States

PA Board of Regents University of Texas System, Austin, TX, United States  
(U.S. corporation)

PI US 5932220 19990803

AI US 1995-437013 19950508 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Ryan, V.

LREP Arnold White & Durkee

CLMN Number of Claims: 26

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 2343

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Bites from *Amblyomma americanum*, a hard tick, have been associated with a Lyme disease-like illness in the southeastern and south-central United States. Present in 2% of ticks collected in four states were uncultivable spirochetes. Through use of the polymerase chain reaction, partial sequences of the flagellin and 16s rRNA genes of microorganisms from Texas and New Jersey were obtained. The sequences showed that the spirochete was a \*\*\**Borrelia*\*\*\* sp. but distinct from other known members of this genus, including *B. burgdorferi*, the agent of Lyme disease. Species-specific differences in the sequences of the flagellin protein, the flagellin gene and the 16s rRNA gene between the new \*\*\**Borrelia*\*\*\* species and previously known species provide compositions and methods for assay for determining the presence of this

new spirochete, or for providing evidence of past or present infection by this spirochete in animal reservoirs and humans.

L7 ANSWER 75 OF 123 USPATFULL

AN 1999:39929 USPATFULL

TI Recombinant retroviruses

IN Guber, Harry E., 13083 Maritime Pl., San Diego, CA, United States 92130

Jolly, Douglas J., 3050 H Via Alicante Dr., La Jolla, CA, United States  
92037

Respass, James G., 4966 Lamont St., San Diego, CA, United States 92109

Laikind, Paul K., 12433 Caminito Mira Del Mar, San Diego, CA, United States 92130

PI US 5888502 19990330

AI US 1995-463122 19950605 (8)

RLI Division of Ser. No. US 1993-136739, filed on 12 Oct 1993, now patented, Pat. No. US 5716826 which is a continuation of Ser. No. US 1989-395932, filed on 18 Aug 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-170515, filed on 21 Mar 1988, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman, Robert

LREP Kruse, Norman J., Pochopien, Donald J., Blackburn, Robert P.

CLMN Number of Claims: 72

ECL Exemplary Claim: 19

DRWN 31 Drawing Figure(s); 27 Drawing Page(s)

LN.CNT 3337

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

L7 ANSWER 76 OF 123 USPATFULL

AN 1999:36949 USPATFULL

TI Engineering oral tissues

IN Mooney, David J., Ann Arbor, MI, United States

Rutherford, Robert B., Ann Arbor, MI, United States

PA The Regents of the University of Michigan, Ann Arbor, MI, United States (U.S. corporation)

PI US 5885829 19990323

AI US 1997-864494 19970528 (8)

PRAI US 1996-18450 19960528 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Degen, Nancy

LREP Arnold, White & Durkee

CLMN Number of Claims: 109

ECL Exemplary Claim: 1

DRWN 17 Drawing Figure(s); 11 Drawing Page(s)

LN.CNT 8001

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are methods for regenerating dental and oral tissues from viable cells using ex vivo culture on a structural matrix. The regenerated oral tissues and tissue-matrix preparations thus provided have both clinical applications in dentistry and oral medicine and are also useful in in vitro toxicity and biocompatibility testing.

L7 ANSWER 77 OF 123 USPATFULL

AN 1999:1776 USPATFULL

TI Hybridomas producing antibodies specific for lyme disease antigens OspA and OspB

IN Simon, Markus M., Freiburg, Germany, Federal Republic of Schaible, Ulrich E., Freiburg, Germany, Federal Republic of Eichmann, Klaus, Freiburg, Germany, Federal Republic of Kramer, Michael, Heidelberg, Germany, Federal Republic of Reinhard, Wallich, Heidelberg, Germany, Federal Republic of

PA Max-Planck-Gesellschaft zur Forderung der Wissenschaften, Heidelberg, Germany, Federal Republic of (non-U.S. corporation)

PI US 5856447 19990105

AI US 1998-27843 19980223

RLI Division of Ser. No. US 1995-406623, filed on 20 Mar 1995 which is a division of Ser. No. US 1993-68063, filed on 27 May 1993, now patented, Pat. No. US 5434077 which is a division of Ser. No. US 1992-937054, filed on 26 Aug 1992, now abandoned which is a division of Ser. No. US 1990-585310, filed on 19 Sep 1990, now patented, Pat. No. US 5178859

PRAI DE 1989-3931236 19890919

DE 1990-4015911 19900517

DT Utility

FS Granted

EXNAM Primary Examiner: Huff, Sheela; Assistant Examiner: Reeves, Julie E.  
LREP Fulbright & Jaworwski

CLMN Number of Claims: 8

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 756

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a \*\*\*vaccine\*\*\* against Lyme disease, wherein it contains one or more monoclonal antibodies which are specific for the 31 kD antigen (OspA) or the 34 kD antigen (OspB) of \*\*\*Borrelia\*\*\* burgdorferi.

The present invention also provides a process for obtaining this \*\*\*vaccine\*\*\*, as well as new monoclonal antibodies, hybridomas and antigens.

L7 ANSWER 78 OF 123 USPATFULL

AN 1999:1521 USPATFULL

TI Method for making reflection defective retroviral vectors for infecting human cells

IN Gruber, Harry E., San Diego, CA, United States  
Jolly, Douglas J., La Jolla, CA, United States

Respass, James G., San Diego, CA, United States  
Laikind, Paul K., San Diego, CA, United States  
Barber, Jack R., San Diego, CA, United States  
St. Louis, Daniel C., Rockville, MD, United States  
Chada, Sunil D., Vista, CA, United States  
Chang, Stephen M. W., San Diego, CA, United States  
Warner, John F., San Diego, CA, United States

PA Chiron Corporation, Emeryville, CA, United States (U.S. corporation)  
PI US 5856185 19990105  
AI US 1995-472109 19950607 (8)

RLI Continuation of Ser. No. US 1994-344743, filed on 23 Nov 1994, now abandoned which is a continuation of Ser. No. US 1993-139994, filed on 20 Oct 1993, now abandoned which is a continuation of Ser. No. US 1992-965084, filed on 22 Oct 1992, now abandoned which is a continuation of Ser. No. US 1990-586603, filed on 21 Sep 1990, now abandoned which is a continuation-in-part of Ser. No. US 1990-565606, filed on 10 Aug 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-395932, filed on 18 Aug 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-170515, filed on 21 Mar 1988, now abandoned

DT Utility  
FS Granted

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman, Robert

LREP Pochopien, Donald, Kruse, Norman J., Blackburn, Robert P.

CLMN Number of Claims: 18

ECL Exemplary Claim: 1

DRWN 54 Drawing Figure(s); 44 Drawing Page(s)

LN.CNT 4588

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

L7 ANSWER 79 OF 123 CABO COPYRIGHT 2002 CABI DUPLICATE 3  
AN 2000:53974 CABO  
DN 20000504583

TI Sensitive and specific serodiagnosis of Lyme disease by enzyme-linked immunosorbent assay with a peptide based on an immunodominant conserved region of \*\*\*Borrelia\*\*\* burgdorferi VlsE

AU Liang FangTing; Steere, A. C.; Marques, A. R.; Johnson, B. J. B.; Miller, J. N.; Philipp, M. T.; Liang, F. T.

CS Department of Parasitology, Tulane Regional Primate Research Center, Tulane University Medical Center, Covington, LA 70433, USA.

SO Journal of Clinical Microbiology, (1999) Vol. 37, No. 12, pp. 3990-3996.  
40 ref.

ISSN: 0095-1137

DT Journal

LA English

AB The diagnostic performance of a peptide ELISA based on a 26-mer synthetic peptide (C6) with the IR6 sequence, an immunodominant conserved region of the variable \*\*\*surface\*\*\* \*\*\*antigen\*\*\* (V1sE) of *B. burgdorferi*, was investigated. Sensitivity was assessed with serum samples (n=210) collected from patients in the USA with clinically defined Lyme disease at the acute (early localized or early disseminated disease), convalescent, or late disease phase. The sensitivities for acute-, convalescent-, and late-phase specimens were 74% (29 of 39), 85-90% (34 of 40 to 35 of 39), and 100% (59 of 59), respectively. Serum specimens from early neuroborreliosis patients were 95% positive (19 of 20), and those from an additional group of patients with posttreatment Lyme disease syndrome yielded a sensitivity of 62% (8 of 13). To assess the specificity of the peptide ELISA, 77 serum samples from patients with other spirochaetal or chronic infections, autoimmune diseases, or neurological diseases and 99 serum specimens from hospitalized patients in an area where Lyme disease is not endemic were examined. Only 2 potential false positives from the hospitalized patients were found, and the overall specificity was 99% (174 of 176). Precision, which was assessed with a panel of positive and negative serum specimens arranged in blinded duplicates, was 100%. Four serum samples with a very high anti-outer surface protein (Osp) A antibody titres obtained from 4 monkeys given the OspA \*\*\*vaccine\*\*\* did not react with the C6 peptide. It is concluded that this simple, sensitive, specific and precise ELISA may contribute to alleviate some of the remaining problems in Lyme disease serodiagnosis. Because of its synthetic peptide base, it will be inexpensive to manufacture. It will also be applicable to serum specimens from Osp-A vaccinated subjects.

L7 ANSWER 80 OF 123 SCISEARCH COPYRIGHT 2002 ISI (R)

AN 1999:164749 SCISEARCH

GA The Genuine Article (R) Number: 168NA

TI *Treponema pallidum* major sheath protein homologue Tpr K is a target of opsonic antibody and the protective immune response

AU CenturionLara A (Reprint); Castro C; Barrett L; Cameron C; Mostowfi M; VanVoorhis W C; Lukehart S A

CS UNIV WASHINGTON, HARBORVIEW MED CTR, DEPT MED, BOX 359779, 325 9TH AVE, SEATTLE, WA 98104 (Reprint)

CY A USA

SO JOURNAL OF EXPERIMENTAL MEDICINE, (15 FEB 1999) Vol. 189, No. 4, pp. 647-656.

Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021.

ISSN: 0022-1007.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 45

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB We have identified a family of genes that code for targets for opsonic antibody and protective immunity in *T. pallidum* subspecies *pallidum* using two different approaches, subtraction hybridization and differential immunologic screening of a *T. pallidum* genomic library. Both approaches led to the identification of a polymorphic multicopy gene family with

predicted amino acid homology to the major sheath protein of *Treponema denticola*. One of the members of this gene family, tpr K, codes for a protein that is predicted to have a cleavable signal peptide and be located in the outer membrane of the bacterium. Reverse transcription polymerase chain reaction analysis of *T. pallidum* reveals that Tpr K is preferentially transcribed in the Nichols strain of *T. pallidum*.

Antibodies directed to purified recombinant variable domain of Tpr K can opsonize *T. pallidum*, Nichols strain, for phagocytosis, supporting the hypothesis that this portion of the protein is exposed at the surface of the treponeme. Immunization of rabbits with the purified recombinant variable domain of Tpr K provides significant protection against infection with the Nichols strain of *T. pallidum*. This gene family is hypothesized to be central to pathogenesis and immunity; during syphilis infection.

L7 ANSWER 81 OF 123 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

DUPLICATE 4

AN 1999:437912 BIOSIS

DN PREV199900437912

TI 1H, 13C, and 15N NMR backbone assignments of 37 kDa \*\*\*surface\*\*\*  
\*\*\*antigen\*\*\* OspC from \*\*\**Borrelia*\*\*\* burgdorferi.

AU Huang, Xiaolin; Link, Karl; Koide, Akiko; Dunn, John J.; Luft, Benjamin  
J.; Koide, Shohei (1)

CS (1) Department of Biochemistry and Biophysics, University of Rochester  
Medical Center, Rochester, NY, 14642 USA

SO Journal of Biomolecular NMR, (July, 1999) Vol. 14, No. 3, pp. 283-284.  
ISSN: 0925-2738.

DT Article

LA English

L7 ANSWER 82 OF 123 CAPLUS COPYRIGHT 2002 ACS

AN 1998:239123 CAPLUS

DN 128:307514

TI \*\*\*Vaccines\*\*\* for infections and cancers

IN Garcon, Nathalie; Friede, Martin

PA Smithkline Beecham Biologicals S.A., Belg.; Garcon, Nathalie; Friede,  
Martin

SO PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9815287	A1	19980416	WO 1997-EP5578	19970930
			W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG	
AU 9747812	A1	19980505	AU 1997-47812	19970930
AU 714930	B2	20000113		
BR 9711853	A	19990824	BR 1997-11853	19970930

EP 939650 A1 19990908 EP 1997-910430 19970930  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, FI  
CN 1238696 A 19991215 CN 1997-180166 19970930  
JP 2001501640 T2 20010206 JP 1998-517196 19970930  
ZA 9708868 A 19990406 ZA 1997-8868 19971003  
NO 9901524 A 19990329 NO 1999-1524 19990329  
KR 2000048866 A 20000725 KR 1999-702874 19990402  
US 2001053365 A1 20011220 US 2001-819464 20010328

PRAI GB 1996-20795 A 19961005

GB 1995-8326 A 19950425  
EP 1996-910019 A 19960401  
WO 1996-EP1464 W 19960401  
WO 1997-EP5578 W 19970930  
US 1997-945450 B2 19971212  
US 1999-269383 W 19990402

AB The invention relates to a \*\*\*vaccine\*\*\* compn. comprising an antigen and an adjuvant compn. for treating infections or cancer. The adjuvant compn. comprises alum, an immunol. active saponin fraction (e.g. QS21) assocd. with liposome contg. a phospholipid and a sterol (e.g. cholesterol), and 3-de-O-acylated monophosphoryl lipid A. The antigen is derived from human immunodeficiency virus, feline immunodeficiency virus, varicella zoster virus, herpes simplex virus type 1 and 2, human cytomegalovirus, hepatitis A, B, C or E, respiratory syncytial virus, human papilloma virus, influenza virus, Hib, meningitis virus, Salmonella, Neisseria, \*\*\*Borrelia\*\*\*, Chlamydia, Bordetella, Plasmodium, Toxoplasma, or cancer.

L7 ANSWER 83 OF 123 USPATFULL

AN 1998:162322 USPATFULL

TI Parasitic helminth asparaginase proteins, nucleic acid molecules, and uses thereof

IN Chandrashekhar, Ramaswamy, Fort Collins, CO, United States

Tsuji, Naotoshi, Fort Collins, CO, United States

PA Heska Corporation, Fort Collins, CO, United States (U.S. corporation)  
Colorado State University Research Foundation, Fort Collins, CO, United States (U.S. corporation)

PI US 5854051 19981229

AI US 1997-929501 19970915 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Patterson, Jr., Charles L.; Assistant Examiner: Nashed, Nashaat T.

LREP Heska CorporationColorado State University Research Foundation

CLMN Number of Claims: 9

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2723

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to: parasitic helminth asparaginase proteins; parasitic helminth asparaginase nucleic acid molecules, including those that encode such asparaginase proteins; antibodies raised against such asparaginase proteins; and compounds that inhibit parasitic helminth asparaginase activity. The present invention also includes methods to obtain such proteins, nucleic acid molecules,

antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to protect animals from diseases caused by parasitic helminths.

L7 ANSWER 84 OF 123 USPATFULL

AN 1998:159468 USPATFULL

TI Recombinant retroviruses

IN Guber, Harry E., 13083 Maritime Pl., San Diego, CA, United States 92130

Jolly, Douglas J., 3050H Via Alicante Dr., La Jolla, CA, United States 92037

Respess, James G., 4966 Lamont St., San Diego, CA, United States 92109

Laikind, Paul K., 12433 Caminito Mira Del Mar, San Diego, CA, United States 92130

PI US 5851529 19981222

AI US 1995-477890 19950607 (8)

RLI Continuation of Ser. No. US 1993-136739, filed on 12 Oct 1993 which is a continuation of Ser. No. US 1989-395932, filed on 18 Aug 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-170515, filed on 21 Mar 1988, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman, Robert

LREP Kruse, Norman J.Seed & Berry, Blackburn, Robert P.

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN 31 Drawing Figure(s); 27 Drawing Page(s)

LN.CNT 3017

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

L7 ANSWER 85 OF 123 USPATFULL

AN 1998:135023 USPATFULL

TI Genetic immunization

IN Weiner, David B., Merion, PA, United States

Williams, William V., Havertown, PA, United States

Wang, Bin, Havertown, PA, United States

PA The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)

The Wistar Institute, Philadelphia, PA, United States (U.S. corporation)

PI US 5830876 19981103

AI US 1995-453349 19950530 (8)

RLI Continuation of Ser. No. US 1993-29336, filed on 11 Mar 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-8342, filed on 26 Jan 1993, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George G.; Assistant Examiner: Railey, II, Johnny F.

LREP Woodcock Washburn Kurtz Mackiewicz & Norris LLP

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 18 Drawing Figure(s); 9 Drawing Page(s)

LN.CNT 2955

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of immunizing an individual against pathogen is disclosed. Also disclosed is a method of treating an individual who has a hyperproliferative disease, or of treating an individual who is infected by a pathogen. Specifically, the individual is injected with bupivacaine along with DNA in an expressible form, the DNA encoding an antigen. The encoded antigen can be from a protein from the pathogen or from a protein associated with the hyperproliferative disease.

L7 ANSWER 86 OF 123 USPATFULL

AN 1998:134622 USPATFULL

TI Method for destroying a diseased human cell

IN Gruber, Harry E., P.O. Box 675272, Rancho Santa Fe, CA, United States 92067

Jolly, Douglas J., 277 Hillcrest Dr., Leucadia, CA, United States 92024  
Respass, James G., 4966 Lamont St., San Diego, CA, United States 92109  
Laikind, Paul K., 3370 Goldfinch St., San Diego, CA, United States 92103

PI US 5830458 19981103

AI US 1995-487776 19950607 (8)

RLI Continuation of Ser. No. US 1993-136739, filed on 12 Oct 1993, now patented, Pat. No. US 5716826 which is a continuation of Ser. No. US 1989-395932, filed on 18 Aug 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-170515, filed on 21 Mar 1988, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George D.; Assistant Examiner: Schwartzman, Robert

LREP Kruse, Norman J., Pochopien, Donald J., Blackburn, Robert P.

CLMN Number of Claims: 38

ECL Exemplary Claim: 1

DRWN 31 Drawing Figure(s); 27 Drawing Page(s)

LN.CNT 3199

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and

pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

L7 ANSWER 87 OF 123 USPATFULL

AN 1998:134621 USPATFULL

TI Recombinant beta-lactamase, usable as carrier molecule in immunogenic compositions

IN Gicquel, Brigitte, Paris, France

Timm, Juliano, Paris, France

Trias, Joaquim, San Mateo, CA, United States

Duez, Colette, Angleur, Belgium

Perilli, Maria-Grazia, L'Aquilie, Italy

Dusart, Jean, Nandrin, Belgium

Frere, Jean-Marie, Nandrin, Belgium

PA Institut Pasteur, Paris Cedex, France (non-U.S. corporation)

PI US 5830457 19981103

WO 9317113 19930902

AI US 1994-284465 19941114 (8)

WO 1993-FR151 19930212

19941114 PCT 371 date

19941114 PCT 102(e) date

PRAI FR 1992-1713 19920214

DT Utility

FS Granted

EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Lau, Kawai

LREP Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

CLMN Number of Claims: 40

ECL Exemplary Claim: 1

DRWN 20 Drawing Figure(s); 20 Drawing Page(s)

LN.CNT 1481

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a nucleotide sequence characterized in that it is selected amongst the following nucleotide sequences: the sequence of the gene coding for a B-lactamase, or any part of said gene, particularly the sequence between nucleotides 1 and 394 containing the signals for expression of the gene, or the coding sequence comprising nucleotides 395 to 1274, or any sequence hybridizing under stringent conditions with the above sequence. Utilization of B-lactamase as a carrier protein for carrying heterolog epitopes for the preparation of \*\*\*vaccine\*\*\* compositions is also disclosed.

L7 ANSWER 88 OF 123 USPATFULL

AN 1998:122388 USPATFULL

TI Genetic immunization

IN Weiner, David B., Merion, PA, United States

Williams, William V., Havertown, PA, United States

Wang, Bin, Havertown, PA, United States

PA The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)

The Wistar Institute, Philadelphia, PA, United States (U.S. corporation)

PI US 5817637 19981006

AI US 1997-783818 19970113 (8)

RLI Continuation of Ser. No. US 1993-125012, filed on 21 Sep 1993, now

patented, Pat. No. US 5593972, issued on 14 Jan 1997 which is a continuation-in-part of Ser. No. US 1993-29336, filed on 11 Mar 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-8342, filed on 26 Jan 1993, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Railey, II, Johnny F.

LREP Woodcock Washburn Kurtz Mackiewicz & Norris LLP

CLMN Number of Claims: 34

ECL Exemplary Claim: 1

DRWN 23 Drawing Figure(s); 12 Drawing Page(s)

LN.CNT 3641

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of prophylactic and therapeutic immunization of an individual against pathogen infection, diseases associated with hyperproliferative cells and autoimmune diseases are disclosed. The methods comprise the steps of administering to cells of an individual, a nucleic acid molecule that comprises a nucleotide sequence that encodes a protein which comprises at least one epitope that is identical or substantially similar to an epitope of a pathogen antigen, a hyperproliferative cell associated protein or a protein associated with autoimmune disease respectively. In each case, nucleotide sequence is operably linked to regulatory sequences to enable expression in the cells. The nucleic acid molecule is free of viral particles and capable of being expressed in said cells. The cells may be contacted cells with a cell stimulating agent. Methods of prophylactically and therapeutically immunizing an individual against HIV are disclosed. Pharmaceutical compositions and kits for practicing methods of the present invention are disclosed.

L7 ANSWER 89 OF 123 USPATFULL

AN 1998:111773 USPATFULL

TI OspE, OspF, and S1 polypeptides in \*\*\*Borrelia\*\*\* burgdorferi

IN Flavell, Richard A., Killingworth, CT, United States

Fikrig, Erol, Guilford, CT, United States

Lam, Tuan T., San Jose, CA, United States

Kantor, Fred S., Orange, CT, United States

Barthold, Stephen W., Madison, CT, United States

PA Yale University, New Haven, CT, United States (U.S. corporation)

PI US 5807685 19980915

AI US 1997-909119 19970811 (8)

RLI Division of Ser. No. US 1993-118469, filed on 8 Sep 1993, now patented,

Pat. No. US 5656451 And a continuation-in-part of Ser. No. US

1993-99757, filed on 30 Jul 1993, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Carlson, Karen

LREP Fish & Neave, Haley, Jr., James F., Gunnison, Jane T.

CLMN Number of Claims: 11

ECL Exemplary Claim: 1

DRWN 17 Drawing Figure(s); 16 Drawing Page(s)

LN.CNT 2343

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the prevention, treatment and diagnosis of

Lyme disease. Novel B. burgdorferi polypeptides, serotypic variants

thereof, fragments thereof and derivatives thereof. Fusion proteins and

multimeric proteins comprising same. Multicomponent \*\*\*vaccines\*\*\* comprising novel *B. burgdorferi* polypeptides in addition to other immunogenic *B. burgdorferi* polypeptides. DNA sequences, recombinant DNA molecules and transformed host cells useful in the compositions and methods. Antibodies directed against the novel *B. burgdorferi* polypeptides, and diagnostic kits comprising the polypeptides or antibodies.

L7 ANSWER 90 OF 123 USPATFULL

AN 1998:82342 USPATFULL

TI Passive \*\*\*vaccine\*\*\* against Lyme disease

IN Simon, Markus M., Freiburg, Germany, Federal Republic of Schaible, Ulrich E., Freiburg, Germany, Federal Republic of Eichmann, Klaus, Freiburg, Germany, Federal Republic of Kramer, Michael, Heidelberg, Germany, Federal Republic of Reinhard, Wallich, Heidelberg, Germany, Federal Republic of

PA Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V., Gottingen, Germany, Federal Republic of (non-U.S. corporation) Deutsches Krebsforschun Zentrum Stiftung des Offentlichen Rechts, Heidelberg, Germany, Federal Republic of (non-U.S. corporation)

PI US 5780030 19980714

AI US 1995-406623 19950320 (8)

RLI Division of Ser. No. US 1993-68063, filed on 27 May 1993, now patented, Pat. No. US 5434077 which is a division of Ser. No. US 1992-937054, filed on 26 Aug 1992, now abandoned which is a division of Ser. No. US 1990-585310, filed on 19 Sep 1990, now patented, Pat. No. US 5178859

PRAI DE 1989-3931236 19890919

DE 1990-4015911 19900517

DT Utility

FS Granted

EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Reeves, Julie E.

LREP Felfe & Lynch

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 811

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a \*\*\*vaccine\*\*\* against Lyme disease, wherein it contains one or more monoclonal antibodies which are specific for the 31 kD antigen (OspA) or the 34 kD antigen (OspB) of \*\*\**Borrelia*\*\*\* *burgdorferi*. The present invention also provides a process for obtaining this \*\*\*vaccine\*\*\*, as well as new monoclonal anti-bodies and antigens.

L7 ANSWER 91 OF 123 USPATFULL

AN 1998:79325 USPATFULL

TI Osp A and B Sequence of \*\*\**Borrelia*\*\*\* *burgdonferi* strains ACA1 and IP90

IN Barbour, Alan George, San Antonio, TX, United States

Bergstrom, Sven, Umea, Sweden

Hansson, Lennart, Umea, Sweden

PA Symbicom Aktiebolag, Umea, Sweden (non-U.S. corporation)

PI US 5777095 19980707

WO 9308306 19930429

AI US 1993-137175 19931026 (8)

WO 1992-US8972 19921022

19931026 PCT 371 date

19931026 PCT 102(e) date

RLI Continuation-in-part of Ser. No. US 1993-79601, filed on 22 Jun 1993,  
now patented, Pat. No. US 5523089 which is a continuation of Ser. No. US  
1992-924798, filed on 6 Aug 1992, now abandoned which is a continuation  
of Ser. No. US 1989-422881, filed on 18 Oct 1989, now abandoned

PRAI DK 1988-5902 19881024

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George G.; Assistant Examiner: Fredman,  
Jeffrey

LREP Curtis, Morris & Safford, Kowalski, Thomas J.

CLMN Number of Claims: 34

ECL Exemplary Claim: 1

DRWN 24 Drawing Figure(s); 22 Drawing Page(s)

LN.CNT 2580

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed and claimed are isolated DNA molecules consisting of  
nucleotide sequences encoding or priming for ospA and/or ospB of various  
B. burgdorferi or portions thereof and methods of making and using the  
same.

L7 ANSWER 92 OF 123 USPATFULL

AN 1998:78723 USPATFULL

TI \*\*\*Vaccine\*\*\* compositions containing 3-O deacylated monophosphoryl  
lipid A

IN Hauser, Pierre, Chaumont-Gistoux, Belgium

Voet, Pierre, Izel, Belgium

Slaoui, Moncef, Rixensart, Belgium

Garcon-Johnson, Nathalie Marie-Josephe Claude, Wavre, Belgium

Desmons, Pierre, Nivelles, Belgium

PA SmithKline Beecham Biologicals (S.A.), Rixensart, Belgium (non-U.S.  
corporation)

PI US 5776468 19980707

WO 9421292 19940929

AI US 1996-525638 19960212 (8)

WO 1994-EP818 19940314

19960212 PCT 371 date

19960212 PCT 102(e) date

PRAI GB 1993-6029 19930323

GB 1994-3417 19940223

DT Utility

FS Granted

EXNAM Primary Examiner: Knodel, Marian C.; Assistant Examiner: Wortman, Donna  
C.

CLMN Number of Claims: 53

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 1493

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel \*\*\*vaccine\*\*\* compositions comprising small particles of  
3-O-deacylated monophosphoryl lipid A are provided. In particular the  
particle size is below 120 nm. Such \*\*\*vaccine\*\*\* compositions have  
superior immunological properties.

L7 ANSWER 93 OF 123 USPATFULL  
AN 1998:75383 USPATFULL  
TI Methods for measurement of lymphocyte function  
IN Wier, Majorie L., Columbia, MD, United States  
PA Biotechnology Transfer, Inc., Columbia, MD, United States (U.S.  
corporation)  
PI US 5773232 19980630  
AI US 1997-928392 19970912 (8)  
RLI Continuation of Ser. No. US 1996-621878, filed on 26 Mar 1996, now  
abandoned  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Smith, Lynette F.; Assistant Examiner: Nelson, Brett  
L.  
LREP Whitham, Curtis & Whitham  
CLMN Number of Claims: 19  
ECL Exemplary Claim: 1  
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)  
LN.CNT 829

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for measuring the responses of sets or subsets of lymphocytes to mitogens or antigens in a sample is disclosed comprising incubating a population of cells with a mitogen or antigen, separating the desired subset of cells by means of the interaction of a specific binding reagent that is attached to the solid phase with a cell surface determinant that is present on the cell subset of interest, lysing the separated cells, and measuring an intracellular component that is increased if the cells have responded to the stimulus. The method provides a convenient, simple, and reliable method for measuring immune function in a variety of conditions.

L7 ANSWER 94 OF 123 USPATFULL  
AN 1998:51196 USPATFULL  
TI \*\*\*Vaccine\*\*\* composition containing adjuvants  
IN Prieels, John Paul, Brussels, Belgium  
Garcon-Johnson, Nathalie Marie-Josephe Claude, Wavre, Belgium  
Slaoui, Moncef, Rixensart, Belgium  
Pala, Pietro, Rixensart, Belgium  
PA SmithKline Beecham Biologicals, s.a, England (non-U.S. corporation)  
PI US 5750110 19980512  
WO 9400153 19940106  
AI US 1995-356372 19950217 (8)  
WO 1993-EP1524 19930615  
19950217 PCT 371 date  
19950217 PCT 102(e) date  
PRAI GB 1992-13559 19920625  
GB 1992-26283 19921217  
GB 1993-4056 19930301  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Smith, Lynette F.  
LREP Kerekes, Zoltan, Lentz, Edward T., Venetianer, Stephen  
CLMN Number of Claims: 26  
ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 530

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides \*\*\*vaccine\*\*\* compositions comprising 3 De-O-acylated monophosphoryl lipid A and QS21. The \*\*\*vaccines\*\*\* compositions are potent inducers of CTL and .gamma. IFN responses.

L7 ANSWER 95 OF 123 USPATFULL

AN 1998:48213 USPATFULL

TI Compositions and methods for the prevention and diagnosis of lyme disease

IN Flavell, Richard A., Killingworth, CT, United States

Kantor, Fred S., Orange, CT, United States

Barthold, Stephen W., Madison, CT, United States

Fikrig, Erol, Guilford, CT, United States

PA Yale University, New Haven, CT, United States (U.S. corporation)

PI US 5747294 19980505

AI US 1994-320161 19941007 (8)

RLI Continuation of Ser. No. US 1991-682355, filed on 8 Apr 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-602551, filed on 26 Oct 1990, now abandoned which is a continuation-in-part of Ser. No. US 1990-538969, filed on 15 Jun 1990, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Loring, Susan A.

LREP Fish & Neave, Haley, Jr., Esq., James F., Gunnison, Esq., Jane T.

CLMN Number of Claims: 9

ECL Exemplary Claim: 3

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 2461

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the prevention and diagnosis of Lyme disease. OspA and OspB polypeptides and serotypic variants thereof, which elicit in a treated animal the formation of an immune response which is effective to treat or protect against Lyme disease as caused by infection with *B. burgdorferi*. Anti-OspA and anti-OspB antibodies that are effective to treat or protect against Lyme disease as caused by infection with *B. burgdorferi*. A screening method for the selection of those OspA and OspB polypeptides and anti-OspA and anti-OspB antibodies that are useful for the prevention and detection of Lyme disease. Diagnostic kits including OspA and OspB polypeptides or antibodies directed against such polypeptides.

L7 ANSWER 96 OF 123 USPATFULL

AN 1998:39510 USPATFULL

TI Compositions and methods for delivery of genetic material

IN Carrano, Richard A., Paoli, PA, United States

Wang, Bin, Beijing, China

Weiner, David B., Merion, PA, United States

PA Apollon, Inc., Malvern, PA, United States (U.S. corporation)

The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)

PI US 5739118 19980414

AI US 1994-221579 19940401 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Rories, Charles C. P.

LREP Woodcock Washburn Kurtz Mackiewicz & Norris, LLP

CLMN Number of Claims: 23

ECL Exemplary Claim: 1

DRWN 8 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 3405

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of introducing genetic material into cells of an individual and compositions and kits for practicing the same are disclosed. The methods comprise the steps of contacting cells of an individual with a genetic \*\*\*vaccine\*\*\* facilitator and administering to the cells, a nucleic acid molecule that is free of retroviral particles. The nucleic acid molecule comprises a nucleotide sequence that encodes a protein that comprises at least one epitope that is identical or substantially similar to an epitope of a pathogen antigen or an antigen associated with a hyperproliferative or autoimmune disease, a protein otherwise missing from the individual due to a missing, non-functional or partially functioning gene, or a protein that produce a therapeutic effect on an individual. Methods of prophylactically and therapeutically immunizing an individual against HIV are disclosed. Pharmaceutical compositions and kits for practicing methods of the present invention are disclosed.

L7 ANSWER 97 OF 123 USPATFULL

AN 1998:14678 USPATFULL

TI Recombinant retroviruses

IN Gruber, Harry E., Rancho Santa Fe, CA, United States

Jolly, Douglas J., Leucadia, CA, United States

Respass, James G., San Diego, CA, United States

Laikind, Paul K., San Diego, CA, United States

PA Chiron Viagene, Inc., United States (U.S. corporation)

PI US 5716826 19980210

AI US 1993-136739 19931012 (8)

RLI Continuation of Ser. No. US 1989-395932, filed on 18 Aug 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-170515, filed on 21 Mar 1988, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George G.; Assistant Examiner: Schwartzman, Robert

LREP Kruse, Norman J.Seed & Berry, Blackburn, Robert P.

CLMN Number of Claims: 8

ECL Exemplary Claim: 1

DRWN 31 Drawing Figure(s); 27 Drawing Page(s)

LN.CNT 2895

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and

pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

L7 ANSWER 98 OF 123 USPATFULL

AN 1998:14473 USPATFULL

TI Recombinant retroviruses

IN Guber, Harry E., San Diego, CA, United States

Jolly, Douglas J., La Jolla, CA, United States

Respass, James G., San Diego, CA, United States

Laikind, Paul K., San Diego, CA, United States

PA Chiron Viagene, Inc., United States (U.S. corporation)

PI US 5716613 19980210

AI US 1995-474736 19950607 (8)

RLI Division of Ser. No. US 1993-136739, filed on 12 Oct 1993 which is a continuation of Ser. No. US 1989-395932, filed on 18 Aug 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-170515, filed on 21 Mar 1988, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George G.; Assistant Examiner: Schwartzman, Robert

LREP Kruse, Norman J.Seed & Berry, Blackburn, Robert P.

CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN 31 Drawing Figure(s); 27 Drawing Page(s)

LN.CNT 2889

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

L7 ANSWER 99 OF 123 USPATFULL

AN 97:115164 USPATFULL

TI Adhesion receptors for pathogenic or opportunistic microorganisms

IN Krivan, Howard C., Derwood, MD, United States

Samuel, James E., Derwood, MD, United States

PA Antex Biologics Inc., Gaithersburg, MD, United States (U.S. corporation)

PI US 5696000 19971209

AI US 1994-275702 19940718 (8)

RLI Continuation of Ser. No. US 1993-78660, filed on 21 Jun 1993, now abandoned which is a division of Ser. No. US 1990-562002, filed on 2 Aug 1990, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Adams, Donald E.; Assistant Examiner: Duffy, Patricia

A.

LREP Pennie & Edmonds

CLMN Number of Claims: 26

ECL Exemplary Claim: 1

DRWN 7 Drawing Figure(s); 4 Drawing Page(s)

LN.CNT 1557

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed herein are receptors for pathogenic or opportunistic microorganisms, methods of obtaining such receptors, and methods of using such receptors for diagnostic or pharmaceutical purposes. The receptor comprises a substantially pure compound selected from the group consisting of GalB1-4GlcNAcB1-3GalB1-4GlcB1-1-X(R), GalB1-3GlcNAcB1-3GalB1-4GlcB1-1-X(R), GlcNAcB1-3GalB1-4GlcB1-1-X(R), GalB1-4GlcNAcB1-3GalB1-4Glc, GalB1-3GlcNAcB1-3GalB1-4Glc, GlcNAcB1-3GalB1-4Glc, GalB1-4GlcNAcB1-3Gal, and GalB1-3-GlcNAcB1-3Gal wherein X is sphingosine, hydroxylated sphingosine, or saturated sphingosine and R is H or an N-acyl fatty acid derivative of X such that X(R) is a ceramide. The invention further comprises proteins and polypeptides that bind to the receptors, methods of obtaining such proteins or polypeptides from natural sources or through recombinant DNA techniques, and methods of using the purified proteins and polypeptides for pharmaceutical and diagnostic purposes, preferably in a \*\*\*vaccine\*\*\* for administration to an animal or human host to protect against pathogenic or opportunistic microorganisms.

L7 ANSWER 100 OF 123 USPATFULL

AN 97:109741 USPATFULL

TI Recombinant retroviruses expressing a protein that converts a pro-drug into a cytotoxic agent

IN Guber, Harry E., 13083 Maritime Pl., San Diego, CA, United States 92130  
Jolly, Douglas J., 3050 Via Alicante Dr., La Jolla, CA, United States 92037

Respass, James G., 4966 Lamont St., San Diego, CA, United States 92109  
Laikind, Paul K., 12433 Caminito Mira Del Mar, San Diego, CA, United States 92130

PI US 5691177 19971125

AI US 1995-460996 19950605 (8)

RLI Division of Ser. No. US 1993-136739, filed on 12 Oct 1993 which is a continuation of Ser. No. US 1989-395932, filed on 18 Aug 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-170515, filed on 21 Mar 1988, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George G.; Assistant Examiner: Railey, II, Johnny F.

LREP Kruse, Norman J., Pochopien, Donald J., Blackburn, Robert P.

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN 31 Drawing Figure(s); 27 Drawing Page(s)

LN.CNT 3039

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the

recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

L7 ANSWER 101 OF 123 USPATFULL

AN 97:107060 USPATFULL

TI Method of selectively destroying neoplastic cells

IN Chiocca, E. Antonio, Boston, MA, United States

Waxman, David J., Newton Centre, MA, United States

Wei, Ming X., Somerville, MA, United States

Breakefield, Xandra O., Newton, MA, United States

Chen, Ling, Brookline, MA, United States

PA The General Hospital Corporation, Boston, MA, United States (U.S. corporation)

Boston University, Boston, MA, United States (U.S. corporation)

Dana-Farber Cancer Institute, Boston, MA, United States (U.S. corporation)

PI US 5688773 19971118

AI US 1994-330523 19941028 (8)

RLI Continuation-in-part of Ser. No. US 1994-291500, filed on 17 Aug 1994, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Stone, Jacqueline M.; Assistant Examiner: Milne, Andrew

LREP Sterne, Kessler, Goldstein & Fox, P.L.L.C.

CLMN Number of Claims: 27

ECL Exemplary Claim: 1

DRWN 46 Drawing Figure(s); 33 Drawing Page(s)

LN.CNT 4282

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for selectively killing nervous system and peripheral neoplastic cells is provided. Viral vectors are used to selectively express a cytochrome P450 gene in neoplastic cells, whose gene product targets the cells for selective killing, by rendering the cells sensitive to a chemotherapeutic agent.

L7 ANSWER 102 OF 123 USPATFULL

AN 97:106805 USPATFULL

TI \*\*\*Borrelia\*\*\* antigen

IN Bergstrom, Sven, Umea, Sweden

Barbour, Alan G., San Antonio, TX, United States

PA Symbicom Aktiebolag, Sweden (non-U.S. corporation)

PI US 5688512 19971118

AI US 1995-375993 19950120 (8)

RLI Division of Ser. No. US 1993-79601, filed on 22 Jun 1993, now patented, Pat. No. US 5523089 which is a continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now abandoned which is a continuation of Ser. No. US 1989-422881, filed on 18 Oct 1989, now abandoned

PRAI DE 1988-5902 19881022

DT Utility

FS Granted

EXNAM Primary Examiner: Sidberry, Hazel F.

LREP Curtis, Morris & Safford, P.C., Kowalski, Thomas J.

CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN 29 Drawing Figure(s); 27 Drawing Page(s)

LN.CNT 2491

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed and claimed are substantially pure OspA, \*\*\*vaccines\*\*\* including substantially pure OspA and an immunologically acceptable carrier or vehicle, methods for producing such \*\*\*vaccines\*\*\*, and methods for inducing a protective immunological response against \*\*\*Borrelia\*\*\* burgdorferi employing such \*\*\*vaccines\*\*\*. The methods for producing the \*\*\*vaccines\*\*\* can include admixing the OspA and the carrier or vehicle. The methods for producing the \*\*\*vaccines\*\*\* also can include recovering the OspA from a host organism transformed with a vector containing DNA encoding the OspA and admixing the OspA with an immunologically acceptable carrier or vehicle. Such methods can further include adding an adjuvant. The \*\*\*vaccine\*\*\* can contain OspA from two or more strains of \*\*\*Borrelia\*\*\* burgdorferi.

L7 ANSWER 103 OF 123 USPATFULL

AN 97:104299 USPATFULL

TI Nucleic acid molecule encoding antigen associated with lyme disease

IN Simon, Markus M., Freiburg, Germany, Federal Republic of Schaible, Ulrich E., Freiburg, Germany, Federal Republic of Eichmann, Klaus, Freiburg, Germany, Federal Republic of Kramer, Michael, Heidelberg, Germany, Federal Republic of Reinhard, Wallich, Heidelberg, Germany, Federal Republic of

PA Max-Planck-Gesellschaft zur Förderung der Wissenschaften E.V., Gottingen, Germany, Federal Republic of (non-U.S. corporation)  
Deutsches Krebsforschung Zentrum Stiftung des Öffentlichen Rechts, Heidelberg, Germany, Federal Republic of (non-U.S. corporation)

PI US 5686267 19971111

AI US 1995-407350 19950320 (8)

RLI Division of Ser. No. US 1993-68063, filed on 27 May 1993, now patented, Pat. No. US 5434077 which is a division of Ser. No. US 1992-937054, filed on 26 Aug 1992, now abandoned which is a division of Ser. No. US 1990-585310, filed on 19 Sep 1990, now patented, Pat. No. US 5178859

PRAI DE 1989-3931236 19890919

DE 1990-4015911 19900517

DT Utility

FS Granted

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Ryan, Verlene

LREP Felfe & Lynch

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 804

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A \*\*\*vaccine\*\*\* against Lyme disease, wherein it contains one or more monoclonal antibodies which are specific for the 31 kD antigen

(OspA) or the 34 kD antigen (OspB) of \*\*\**Borrelia*\*\*\* *burgdorferi*.  
The present invention also provides a process for obtaining this  
\*\*\*vaccine\*\*\* , as well as new monoclonal antibodies and antigens.

L7 ANSWER 104 OF 123 USPATFULL

AN 97:104145 USPATFULL

TI Microcapsules of predetermined peptide(s) specificity (ies), their preparation and uses

IN Speaker, Tully J., Philadelphia, PA, United States  
Sultzbaugh, Kenneth J., Philadelphia, PA, United States

PA Temple University of the Commonwealth System of Higher Education, Philadelphia, PA, United States (U.S. corporation)

PI US 5686113 19971111

AI US 1995-408052 19950321 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Nutter, Nathan M.

LREP Ratner & Prestia

CLMN Number of Claims: 42

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1708

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An aqueous core microcapsule has a capsular wall provided with a peptide(s) of pre-determined binding specificity(ies) appended to the surface, the wall being the reaction product of an anionic polymer or salt thereof and a polyamine, salt thereof, mixtures thereof, or mixtures thereof with monoamines. The aqueous core may contain an active ingredient(s), and be targeted for delivery to specific cell tissues.  
The microcapsules are provided as a composition and in a kit with instructions for use in imaging, diagnosis, therapy, vaccination, and other applications.

L7 ANSWER 105 OF 123 USPATFULL

AN 97:70893 USPATFULL

TI OspE, OspF, and S1 polypeptides in \*\*\**borrelia*\*\*\* *burgdorferi*

IN Flavell, Richard A., Killingworth, CT, United States

Fikrig, Erol, Guilford, CT, United States

Lam, Tuan T., San Jose, CA, United States

Kantor, Fred S., Orange, CT, United States

Barthold, Stephen W., Madison, CT, United States

PA Yale University, New Haven, CT, United States (U.S. corporation)

PI US 5656451 19970812

AI US 1993-118469 19930908 (8)

RLI Continuation-in-part of Ser. No. US 1993-99757, filed on 30 Jul 1993,  
now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Carlson, K.  
Cochrane

LREP Fish & Neave, Haley, Jr. Esq., James F., Gunnison, Esq., Jane T.

CLMN Number of Claims: 9

ECL Exemplary Claim: 1

DRWN 17 Drawing Figure(s); 16 Drawing Page(s)

LN.CNT 2447

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the prevention, treatment and diagnosis of Lyme disease. Novel *B. burgdorferi* polypeptides, serotypic variants thereof, fragments thereof and derivatives thereof. Fusion proteins and multimeric proteins comprising same. Multicomponent \*\*\*vaccines\*\*\* comprising novel *B. burgdorferi* polypeptides in addition to other immunogenic *B. burgdorferi* polypeptides. DNA sequences, recombinant DNA molecules and transformed host cells useful in the compositions and methods. Antibodies directed against the novel *B. burgdorferi* polypeptides, and diagnostic kits comprising the polypeptides or antibodies.

L7 ANSWER 106 OF 123 USPATFULL

AN 97:3820 USPATFULL

TI Genetic immunization

IN Weiner, David B., Merion, PA, United States

Williams, William V., Havertown, PA, United States

Wang, Bin, Havertown, PA, United States

PA The Wistar Institute, Philadelphia, PA, United States (U.S. corporation)

The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)

PI US 5593972 19970114

AI US 1993-125012 19930921 (8)

RLI Continuation-in-part of Ser. No. US 1993-29336, filed on 11 Mar 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-8342, filed on 26 Jan 1993, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Fleisher, Mindy; Assistant Examiner: Railey, II, Johnny F.

LREP Woodcock Washburn Kurtz Mackiewicz & Norris

CLMN Number of Claims: 9

ECL Exemplary Claim: 1

DRWN 23 Drawing Figure(s); 12 Drawing Page(s)

LN.CNT 3611

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of prophylactic and therapeutic immunization of an individual against pathogen infection, diseases associated with hyperproliferative cells and autoimmune diseases are disclosed. The methods comprise the steps of administering to cells of an individual, a nucleic acid molecule that comprises a nucleotide sequence that encodes a protein which comprises at least one epitope that is identical or substantially similar to an epitope of a pathogen antigen, a hyperproliferative cell associated protein or a protein associated with autoimmune disease respectively. In each case, nucleotide sequence is operably linked to regulatory sequences to enable expression in the cells. The nucleic acid molecule is free of viral particles and capable of being expressed in said cells. The cells may be contacted cells with a cell stimulating agent. Methods of prophylactically and therapeutically immunizing an individual against HIV are disclosed. Pharmaceutical compositions and kits for practicing methods of the present invention are disclosed.

L7 ANSWER 107 OF 123 USPATFULL

AN 97:1353 USPATFULL

TI Method of determining the presence of endotoxin in a sample

IN B.ae butted.k, Leif, Heinesgade 1, 4.tv., 2200 Copenhagen N, Denmark  
Koch, Claus, Overgaden oven Van-det 26.1, 1415 Copenhagen, Denmark  
PI US 5591628 19970107  
AI US 1990-68178 19900528 (8)  
RLI Division of Ser. No. US 1989-295213, filed on 6 Jan 1989, now patented,  
Pat. No. US 5316911  
PRAI DK 1987-2558 19870520  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Nucker, Christine M.; Assistant Examiner: Stucker,  
Jeffrey  
LREP Birch, Stewart, Kolasch & Birch, LLP  
CLMN Number of Claims: 27  
ECL Exemplary Claim: 1  
DRWN 10 Drawing Figure(s); 10 Drawing Page(s)  
LN.CNT 1825  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB There is disclosed a method for determining the presence of endotoxin or  
an endotoxin like substance in a sample, as well as a monoclonal  
antibody and test kit useful in the method.

L7 ANSWER 108 OF 123 USPATFULL  
AN 96:113791 USPATFULL  
TI DNA encoding \*\*\*borrelia\*\*\* burgdorferi OspA and a method for  
diagnosing \*\*\*borrelia\*\*\* burgdorferi infection  
IN Bergstrom, Sven, Umea, Sweden  
Barbour, Alan G., San Antonio, TX, United States  
Magnarelli, Louis A., Durham, CT, United States  
PA Symbicomb Aktiebolag, Sweden (non-U.S. corporation)  
PI US 5582990 19961210  
AI US 1994-320416 19941003 (8)  
RLI Division of Ser. No. US 1993-76601, filed on 22 Jun 1993 which is a  
continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now  
abandoned which is a continuation of Ser. No. US 1989-422881, filed on  
18 Oct 1989, now abandoned

PRAI DK 1988-5902 19881024

DT Utility

FS Granted

EXNAM Primary Examiner: Jones, W. Gary; Assistant Examiner: Arthur, Lisa B.  
LREP Curtis, Morris & Safford, Kowalski, Thomas J.  
CLMN Number of Claims: 12  
ECL Exemplary Claim: 1  
DRWN 25 Drawing Figure(s); 24 Drawing Page(s)  
LN.CNT 2569

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed and claimed are isolated nucleic acid molecules, such as DNA  
encoding \*\*\*Borrelia\*\*\* burgdorferi OspA, vectors containing the  
nucleic acid molecules, and methods for diagnosing \*\*\*Borrelia\*\*\*  
burgdorferi infection employing such nucleic acid molecules. The  
isolated nucleic acid molecule can be an isolated DNA molecule encoding  
the 31 kD OspA protein of New York strain B31. The isolated nucleic acid  
molecule also can be an isolated DNA molecule encoding \*\*\*Borrelia\*\*\*  
burgdorferi OspA and a signal peptide which contains an amino acid  
recognition sequence. The recognition sequence can be L-z-z-C, where  
each z independently designates a small, neutral amino acid, such as

isoleucine or alanine. The recognition sequence can also be L-I-x-C where x is a non-charged amino acid residue, such as alanine. Further, the isolated nucleic acid molecule can be an isolated DNA molecule encoding \*\*\*Borrelia\*\*\* burgdorferi OspA and which includes a 5'-flanking region containing at least one promoter sequence for expression of the OspA. And additionally, the isolated nucleic acid molecule can be an isolated DNA molecule encoding \*\*\*Borrelia\*\*\* burgdorferi OspA as a fusion polypeptide containing the OspA.

L7 ANSWER 109 OF 123 USPATFULL

AN 96:113637 USPATFULL

TI Sonicated \*\*\*borrelia\*\*\* burgdorferi \*\*\*vaccine\*\*\*

IN Alliger, Howard M., Melville, NY, United States

Frey, Alan, Highland Park, NJ, United States

PA Rx Technologies, Inc., Garden City, NY, United States (U.S. corporation)

PI US 5582829 19961210

AI US 1992-921303 19920728 (7)

RLI Continuation-in-part of Ser. No. US 1990-505193, filed on 5 Apr 1990,  
now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Krsek-Staples,  
Julie

LREP Coleman, Henry D., Sudol, R. Neil

CLMN Number of Claims: 16

ECL Exemplary Claim: 7

DRWN 7 Drawing Figure(s); 7 Drawing Page(s)

LN.CNT 1175

AB A process for the preparation of a \*\*\*vaccine\*\*\* from substantially viable spirochetal bacteria of \*\*\*Borrelia\*\*\*, preferably \*\*\*Borrelia\*\*\* burgdorferi having immunogenic or therapeutic properties and capable of inducing an immune or therapeutic response against Lyme Disease when administered to a patient is described. The product for use against Lyme Disease is produced by ultrasound treatment of substantially viable spirochetal bacteria of \*\*\*Borrelia\*\*\* burgdorferi. The invention produces a product and a method of treatment that can be used for the immunization and/or therapy of a patient against Lyme Disease to minimize or prevent the contraction of the disease or to treat the disease.

L7 ANSWER 110 OF 123 USPATFULL

AN 96:55858 USPATFULL

TI Method for the purification of PC protein from \*\*\*Borrelia\*\*\*  
burgdorferi

IN Livey, Ian, Vienna, Austria

Dorner, Friedrich, Vienna, Austria

PA Immuno Aktiengesellschaft, Vienna, Austria (non-U.S. corporation)

PI US 5530103 19960625

AI US 1993-31295 19930312 (8)

RLI Division of Ser. No. US 1992-903580, filed on 25 Jun 1992 which is a continuation-in-part of Ser. No. US 1992-824161, filed on 22 Jan 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-727245, filed on 11 Jul 1991, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Krsek-Staples,

Julie

LREP Foley & Lardner

CLMN Number of Claims: 1

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 1039

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of purifying *B. burgdorferi* proteins comprising the steps of  
(a) disrupting a *B. burgdorferi* cell and fractionating the disrupted  
cell into membrane and cytoplasmic components; (b) resuspending the  
membrane component in a non-denaturing detergent thereby producing a  
solubilized protein and an insolubilized material and then separating  
said solubilized protein from said insolubilized material; (c)  
subjecting the solubilized protein to ion-exchange chromatography so as  
to produce protein fractions; and (d) assaying the protein fractions to  
identify those fractions which contain proteins of interest wherein the  
purified proteins of interest are in a biologically active form suitable  
for use in \*\*\*vaccines\*\*\* , is disclosed.

L7 ANSWER 111 OF 123 USPATFULL

AN 96:48180 USPATFULL

TI \*\*\**Borrelia*\*\*\* antigen

IN Bergstrom, Sven, Umea, Sweden

Barbour, Alan G., San Antonio, TX, United States

Magnarelli, Louis A., Durham, CT, United States

PA Symbicom Aktiebolag, Sweden (non-U.S. corporation)

PI US 5523089 19960604

AI US 1993-79601 19930622 (8)

RLI Continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now  
abandoned which is a continuation of Ser. No. US 1989-422881, filed on  
18 Oct 1989, now abandoned

PRAI DK 1988-5902 19881024

DT Utility

FS Granted

EXNAM Primary Examiner: Sidberry, Hazel F.

LREP Curtis, Morris & Safford, Kowalski, Thomas J.

CLMN Number of Claims: 21.

ECL Exemplary Claim: 1

DRWN 24 Drawing Figure(s); 24 Drawing Page(s)

LN.CNT 2671

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB B fraction of \*\*\**Borrelia*\*\*\* *burgdorferi*, methods for preparing the  
B fraction, and compositions containing the B fraction, are disclosed  
and claimed.

L7 ANSWER 112 OF 123 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

DUPLICATE 5

AN 1995:79777 BIOSIS

DN PREV199598094077

TI Epitopes on \*\*\*surface\*\*\* \*\*\*antigens\*\*\* other than OspA can  
elicit a bactericidal effect against Lyme disease \*\*\*borrelia\*\*\* .

AU Shoberg, Russell J. (1); Thomas, D. Denee

CS (1) Dep. Periodontics, Univ. Tex. Health Sci. Cent. San Antonio, 7703

Floyd Curl Drive, San Antonio, TX 78284-7894 USA

SO Journal of Infectious Diseases, (1995) Vol. 171, No. 1, pp. 253-254.

ISSN: 0022-1899.

DT Letter

LA English

L7 ANSWER 113 OF 123 USPATFULL

AN 95:64847 USPATFULL

TI \*\*\*Borrelia\*\*\* burgdorferi strain 257

IN Simon, Markus M., Freiburg, Germany, Federal Republic of  
Schaible, Ulrich E., Freiburg, Germany, Federal Republic of  
Eichmann, Klaus, Freiburg, Germany, Federal Republic of  
Kramer, Michael, Heidelberg, Germany, Federal Republic of  
Reinhard, Wallich, Heidelberg, Germany, Federal Republic of

PA Max-Planck-Gesellschaft zur Forderung der Wissenschaften e.V.,  
Gottingen, Germany, Federal Republic of (non-U.S. corporation)  
Deutsches Krebsforschungszentrum Stiftung des Offentlichen Rechts,  
Heidelberg, Germany, Federal Republic of (non-U.S. corporation)

PI US 5434077 19950718

AI US 1993-68063 19930527 (8)

RLI Division of Ser. No. US 1992-937054, filed on 26 Aug 1992, now abandoned  
which is a division of Ser. No. US 1990-585310, filed on 19 Sep 1990,  
now patented, Pat. No. US 5178859

PRAI DE 1989-39312364 19890919

DE 1990-40159116 19900517

DT Utility

FS Granted

EXNAM Primary Examiner: Sidberry, Hazel F.

LREP Felfe & Lynch

CLMN Number of Claims: 1

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 785

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a \*\*\*vaccine\*\*\* against Lyme disease,  
wherein it contains one or more monoclonal antibodies which are specific  
for the 31 kD antigen (OspA) or the 34 kD antigen (OspB) of  
\*\*\*Borrelia\*\*\* burgdorferi.

The present invention also provides a process for obtaining this  
\*\*\*vaccine\*\*\*, as well as new monoclonal antibodies and antigens.

L7 ANSWER 114 OF 123 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 95016838 EMBASE

DN 1995016838

TI Epitopes on \*\*\*surface\*\*\* \*\*\*antigens\*\*\* other than OspA can  
elicit a bactericidal effect against Lyme disease \*\*\*borrelia\*\*\* [2].

AU Shoberg R.J.; Thomas D.D.

CS Dept. of Periodontics, Texas Univ. Health Science Center, 7703 Floyd Curl  
Dr., San Antonio, TX 78284-7894, United States

SO Journal of Infectious Diseases, (1995) 171/1 (253-254).

ISSN: 0022-1899 CODEN: JIDIAQ

CY United States

DT Journal; Letter

FS 004 Microbiology

026 Immunology, Serology and Transplantation

037 Drug Literature Index  
LA English

L7 ANSWER 115 OF 123 USPATFULL

AN 94:46868 USPATFULL

TI Method of determining the presence of endotoxin in a sample

IN Baek, Leif, Heinesgade 1, 4.tv., 2200 Copenhagen N, Denmark

Koch, Claus, Overgaden oven Vandet 26, 1., 1415 Copenhagen K, Denmark

PI US 5316911 19940531

WO 8809507 19881201

AI US 1989-295213 19890106 (7)

WO 1988-DE81 19880519

19890106 PCT 371 date

19890106 PCT 102(e) date

PRAI DK 1987-2558 19870520

DT Utility

FS Granted

EXNAM Primary Examiner: Rosen, Sam

LREP Birch, Stewart, Kolasch & Birch

CLMN Number of Claims: 29

ECL Exemplary Claim: 1,2

DRWN 10 Drawing Figure(s); 10 Drawing Page(s).

LN.CNT 1845

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In a method of determining the presence of an endotoxin or endotoxin-like material in a sample, a) a sample is incubated with a component of horseshoe crab amoebocytes lysate or haemolymph or a synthetic analogue thereof, b) the incubated mixture of the sample and the component or analogue resulting from step a) is reacted with an antibody raised against the component or analogue or against a reaction product of the incubation of step a), and c) the presence of endotoxin or endotoxin-like material in the sample is determined by detecting any bound antibody in the reaction mixture of step b). In the method either the component or analogue or the antibody or the endotoxin or endotoxin-like material is coupled to a solid support.

L7 ANSWER 116 OF 123 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1994:547350 BIOSIS

DN PREV199598006898

TI \*\*\*Borrelia\*\*\* burgdorferi Antigens That Are Targeted by Antibody-Dependent, Complement-Mediated Killing in the Rhesus Monkey.

AU Aydintug, M. Kemal; Gu, Yan; Philipp, Mario T. (1)

CS (1) Dep. Parasitol., Tulane Regional Primate Res. Cent., Tulane Univ. Med. Cent., Covington, LA 70433 USA

SO Infection and Immunity, (1994) Vol. 62, No. 11, pp. 4929-4937.

ISSN: 0019-9567.

DT Article

LA English

AB We identified \*\*\*surface\*\*\* \*\*\*antigens\*\*\* of \*\*\*Borrelia\*\*\* burgdorferi that are targeted by antibody-dependent, complement-mediated killing (ADCK) in the rhesus monkey. For this purpose, we had available serum samples from three animals infected with B. burgdorferi JD1 by needle inoculation and from two monkeys that were infected with the same B. burgdorferi strain by Ixodes scapularis tick bite. Sera from monkeys from the first group contained antibodies to OspA and OspB detectable by

Western blot (immunoblot) using whole *B. burgdorferi* antigens, whereas serum samples from animals in the second group did not. The targeting of OspA and OspB by functional antibodies was demonstrated directly by showing that ADCK was partially inhibited when antibodies were preincubated with an excess of soluble recombinant OspA or OspB. Simultaneous addition of OspA and OspB did not result in an additive inhibitory effect on ADCK, a result that suggests that the epitopes on OspA and that on OspB targeted by antibody in this mechanism are the same, or at least cross-reacting. The targeting of non-OspA, non-OspB \*\*\*surface\*\*\* \*\*\*antigens\*\*\* was inferred from the fact that sera from tick-inoculated animals, which did not contain detectable anti-OspA or anti-OspB antibodies, were able to effect ADCK. This killing effect was not inhibitible by the addition of recombinant OspA or OspB or both proteins together. We also showed that both immunoglobulin G and M antibodies participate in the ADCK mechanism in the rhesus monkey. Rhesus complement does not kill *B. burgdorferi* in vitro in the absence of antibody, and antibody alone is effective in killing only at serum dilutions lower than 1:15. However, such "complementindependent" antibodies were not present in all bleeds. Two main conclusions may be drawn from the analysis of our results. First, both OspA and OspB are targeted by the ADCK mechanism in the rhesus monkey. Second, one or more *B. burgdorferi* \*\*\*surface\*\*\* \*\*\*antigens\*\*\* that are neither OspA nor OspB also participate in ADCK.

L7 ANSWER 117 OF 123 CAPLUS COPYRIGHT 2002 ACS

AN 1993:249317 CAPLUS

DN 118:249317

TI Bacterial expression vectors containing DNA encoding secretion signals of lipoproteins and their uses for preparation of \*\*\*vaccines\*\*\*

IN Stover, Charles K.

PA Medimmune, Inc., USA

SO PCT Int. Appl., 115 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 9307897 A1 19930429 WO 1992-US9075 19921021

W: AU, CA, JP

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE

AU 9229110 A1 19930521 AU 1992-29110 19921021

AU 681572 B2 19970904

EP 625052 A1 19941123 EP 1992-923207 19921021

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE

JP 07502646 T2 19950323 JP 1992-507931 19921021

PRAI US 1991-780261 19911021

WO 1992-US9075 19921021

AB A bacterial expression vector contg. a DNA encoding the secretion signal of a lipoprotein and a heterologous protein antigen is prep'd. The expression vector increases the immunogenicity of the protein by enabling the presentation of the protein on the surface of the bacterial host.

Transformed bacteria expressing a chimeric gene for a fusion protein of

the lipoprotein and the antigen protein can be used in a \*\*\*vaccine\*\*\*

. Mycobacterium such as BCG may be transformed with a plasmid vector

encoding an Outer Surface Protein A or B of \*\*\*Borrelia\*\*\* burgdorferi and used in \*\*\*vaccines\*\*\* against Lyme disease. Construction of plasmids, e.g. p2619::OspA, contg. the BCG HSP60 gene promoter, the signal sequence of the 19-kDa antigen of M. tuberculosis, and the OspA antigen was demonstrated. Immunization of mice with the BCG transformed with plasmids was also shown.

L7 ANSWER 118 OF 123 USPATFULL

AN 93:78691 USPATFULL

TI Virulence associated proteins in \*\*\*Borrelia\*\*\* burgdorferi (BB)

IN Norris, Steven J., Houston, TX, United States

Barbour, Alan G., San Antonio, TX, United States

PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)

PI US 5246844 19930921

AI US 1991-781355 19911022 (7)

DT Utility

FS Granted

EXNAM Primary Examiner: Nucker, Christine M.; Assistant Examiner: Dubrule, Chris

LREP Arnold, White & Durkee

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN 10 Drawing Figure(s); 14 Drawing Page(s)

LN.CNT 1705

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a DNA segment encoding a \*\*\*Borrelia\*\*\* burgdorferi antigenic polypeptide. The invention also relates to a purified 30 kDa polypeptide isolated from a virulent strain of B. burgdorferi and to epitopic segments of the polypeptide with immunogenic potential. The 30 kDa protein provides a route for the development of immunodiagnostics for Lyme disease and related disorders. The 30 kDa protein and related amino acid and DNA sequences may also be used for the immunization, for the detection of B. burgdorferi in human or animal tissues or body fluids, and also for the generation of specific antibodies for use in diagnosis, epidemiology, and prevention of Lyme disease.

L7 ANSWER 119 OF 123 USPATFULL

AN 93:3341 USPATFULL

TI \*\*\*Vaccine\*\*\* against Lyme disease

IN Simon, Markus M., Freiburg, Germany, Federal Republic of Schaible, Ulrich E., Freiburg, Germany, Federal Republic of Eichmann, Klaus, Freiburg, Germany, Federal Republic of Kramer, Michael, Heidelberg, Germany, Federal Republic of Reinhard, Wallich, Heidelberg, Germany, Federal Republic of

PA Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V., Gottingen, Germany, Federal Republic of (non-U.S. corporation) Deutsches Krebsforschungszentrum Stiftung des öffentlichen Rechts, Heidelberg, Germany, Federal Republic of (non-U.S. corporation)

PI US 5178859 19930112

AI US 1990-585310 19900919 (7)

PRAI DE 1989-3931236 19890919

DE 1990-4015911 19900517

DT Utility

FS Granted

EXNAM Primary Examiner: Nucker, Christine M.; Assistant Examiner: Sidberry, H.

F.

LREP Felfe & Lynch

CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 756

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a \*\*\*vaccine\*\*\* against Lyme disease, wherein it contains one or more monoclonal antibodies which are specific for the 31 kD antigen (OspA) or the 34 kD antigen (OspB) of \*\*\*Borrelia\*\*\* burgdorferi.

The present invention also provides a process for obtaining this \*\*\*vaccine\*\*\*, as well as new monoclonal antibodies and antigens.

L7 ANSWER 120 OF 123 SCISEARCH COPYRIGHT 2002 ISI (R)

AN 93:176707 SCISEARCH

GA The Genuine Article (R) Number: KR822

TI MULTIPLE GENES ENCODE THE MAJOR SURFACE GLYCOPROTEIN OF PNEUMOCYSTIS-CARINII

AU KOVACS J A (Reprint); POWELL F; EDMAN J C; LUNDGREN B; MARTINEZ A; DREW B; ANGUS C W

CS NIH, CTR CLIN, DEPT CRIT CARE MED, BLDG 10, RM 7D43, 9000 ROCKVILLE PIKE, BETHESDA, MD, 20892 (Reprint); UNIV CALIF SAN FRANCISCO, HORMONE RES INST, SAN FRANCISCO, CA, 94143; UNIV CALIF SAN FRANCISCO, LAB MED LAB, SAN FRANCISCO, CA, 94143

CYA USA

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (15 MAR 1993) Vol. 268, No. 8, pp. 6034-6040.

ISSN: 0021-9258.

DT Article; Journal

FS LIFE

LA ENGLISH

REC Reference Count: 47

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The major \*\*\*surface\*\*\* \*\*\*antigen\*\*\* of *Pneumocystis carinii*, a life-threatening opportunistic pathogen in human immunodeficiency virus-infected patients, is an abundant glycoprotein that functions in host-organism interactions. A monoclonal antibody to this antigen is protective in animals, and thus this antigen is a good candidate for development as a \*\*\*vaccine\*\*\* to prevent or control *P. carinii* infection. We have cloned and sequenced seven related but unique genes encoding the major surface glycoprotein of rat *P. carinii*. Partial amino acid sequencing confirmed the identity of these genes. Based on Southern blot studies using chromosomal or restricted DNA, the major surface glycoproteins are the products of a multicopy family of genes. The predicted protein has an M(r) of approximately 123,000, is relatively rich in cysteine residues (5.5%) that are very strongly conserved, and contains a well conserved hydrophobic region at the carboxyl terminus. The presence of multiple related msg genes encoding the major surface glycoprotein of *P. carinii* suggests that antigenic variation is a possible mechanism for evading host defenses. Further characterization of this family of genes should allow the development of novel approaches to the control of this

pathogen.

L7 ANSWER 121 OF 123 CABA COPYRIGHT 2002 CABI DUPLICATE 6

AN 95:121298 CABA

DN 950503945

TI Protective immunity in Lyme \*\*\*borreliosis\*\*\*

AU Fikrig, E.; Kantor, F. S.; Barthold, S. W.; Flavell, R. A.

CS Section of Rheumatology, Yale University School of Medicine, New Haven, CT 06510, USA.

SO Parasitology Today, (1993) Vol. 9, No. 4, pp. 129-131. 35 ref.

DT Journal

LA English

AB The use of \*\*\*Borrelia\*\*\* burgdorferi \*\*\*surface\*\*\*

\*\*\*antigens\*\*\* as \*\*\*vaccine\*\*\* candidates for Lyme disease is discussed. A murine model of \*\*\*Borrelia\*\*\* in the immunocompetent C3H mouse mimics features of human Lyme disease, and this has made it a very useful model for the study of protective immunity to \*\*\*Borrelia\*\*\* infection. When vaccinated mice were challenged with \*\*\*Borrelia\*\*\* up to 4 months after immunization, and sacrificed 6 months after challenge infection, protection was seen to be complete. However, strain variability among \*\*\*Borrelia\*\*\* isolates has been reported and studies to develop a taxonomic classification system are progressing. The heterogeneity of \*\*\*Borrelia\*\*\* is discussed, as well as immunization against vector-borne Lyme \*\*\*borreliosis\*\*\*.

L7 ANSWER 122 OF 123 CAPLUS COPYRIGHT 2002 ACS

AN 1993:406746 CAPLUS

DN 119:6746

TI A recombinant \*\*\*vaccine\*\*\* for Lyme disease

AU Fikrig, E.; Barthold, S. W.; Sears, J. E.; Teford, S. R., III; Spielman, A.; Kantor, F. S.; Flavell, R. A.

CS Sch. Med., Yale Univ., New Haven, CT, 06510, USA

SO Curr. Commun. Cell Mol. Biol. (1992), 6(Lyme Disease: Molecular and Immunologic Approaches), 263-82

CODEN: CCCBEL

DT Journal

LA English

AB A discussion is presented on the usefulness of \*\*\*Borrelia\*\*\*

burgdorferi \*\*\*surface\*\*\* \*\*\*antigens\*\*\* as candidates for a \*\*\*vaccine\*\*\* against Lyme disease.

L7 ANSWER 123 OF 123 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

DUPLICATE 7

AN 1990:309570 BIOSIS

TI MONOCLONAL ANTIBODIES SPECIFIC FOR THE OUTER SURFACE PROTEIN A OSPA OF \*\*\*BORRELIA\*\*\* -BURGDORFERI PREVENT LYME \*\*\*BORRELIOSIS\*\*\* IN SEVERE COMBINED IMMUNODEFICIENCY SCID MICE.

AU SCHAIBLE U E; KRAMER M D; EICHMANN K; MODOLELL M; MUSETEANU C; SIMON M M

CS MAX-PLANCK-INST. IMMUNBIOL., STUEBEWEG 51, D-7800 FREIBURG, FRG.

SO PROC NATL ACAD SCI U S A, (1990) 87 (10), 3768-3772.

CODEN: PNASA6. ISSN: 0027-8424.

FS BA; OLD

LA English

AB We have recently shown that viable \*\*\*Borrelia\*\*\* burgdorferi organisms induce a chronic infection associated with arthritis and

carditis in severe combined immunodeficiency (scid) mice but not in immunocompetent mice. The disease is similar to that found in patients suffering from Lyme disease. We now show that *B. burgdorferi*-specific immune mouse sera as well as monoclonal antibody to the spirochetal outer \*\*\*surface\*\*\* \*\*\*antigen\*\*\* A (31 kDa) but not monoclonal antibodies specific for the 41-kDa antigenic component of the periplasmic flagella are able to prevent (or mitigate) the development of the disease in scid mice when passively transferred at the time of the bacterial inoculation. The identification of a *B. burgdorferi*-associated protective antigen suggests that the corresponding spirochetal protein should be tested as a \*\*\*vaccine\*\*\* against Lyme disease.

=> s (borrelia burgdorferi sensu lato)  
L11 1615 (BORRELIA BURGDORFERI SENSU LATO)

=> s 111 and review  
L12 49 L11 AND REVIEW

=> dup rem 112  
PROCESSING COMPLETED FOR L12  
L13 29 DUP REM L12 (20 DUPLICATES REMOVED)

=> d bib ab 1-  
YOU HAVE REQUESTED DATA FROM 29 ANSWERS - CONTINUE? Y/(N):y

L13 ANSWER 1 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.  
AN 2002053003 EMBASE

TI Host association of \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\*  
\*\*\*lato\*\*\* - The key role of host complement.

AU Kurtenbach K.; De Michelis S.; Etti S.; Schafer S.M.; Sewell H.-S.; Brade V.; Kraiczy P.

CS K. Kurtenbach, Dept. of Infect. Dis. Epidemiology, Imperial Coll. of Sci.,  
Tech./Med., St Mary's Campus, Norfolk Place, London W2 1PG, United  
Kingdom. k.kurtenbach@ic.ac.uk

SO Trends in Microbiology, (1 Feb 2002) 10/2 (74-79).

Refs: 51

ISSN: 0966-842X CODEN: TRMIEA

PUI S 0966-842X(01)02298-3

CY United Kingdom

DT Journal; General Review

FS 004 Microbiology

LA English

SL English

AB \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\*

(s.l.), the tick-borne agent of Lyme borreliosis, is a bacterial species complex comprising 11 genospecies. Here, we discuss whether the delineation of genospecies is ecologically relevant. We provide evidence that *B. burgdorferi* s.l. is structured ecologically into distinct clusters that are host specific. An immunological model for niche adaptation is proposed that suggests the operation of complement-mediated selection in the midgut of the feeding tick. We conclude that vertebrate hosts rather than tick species are the key to Lyme borreliosis spirochaete diversity.

Q R 1. T 7, *adonis*

L13 ANSWER 2 OF 29 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1

AN 2002:15223 CAPLUS  
TI Lyme disease and current aspects of immunization  
AU Kamradt, Thomas  
CS Deutsches Rheumaforchungszentrum Berlin, Medizinische Universitätsklinik,  
Berlin, Germany  
SO Arthritis Research [online computer file] (2002), 4(1), 20-29  
CODEN: ARESFU; ISSN: 1465-9913  
URL: <http://arthritis-research.com/content/pdf/AR-4-1-20.pdf>  
PB BioMed Central Ltd.  
DT Journal; (online computer file)  
LA English  
AB Lyme disease is a tick-borne multisystem disease that affects primarily the skin, nervous system, heart and joints. At least three species of \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\*, namely Borrelia burgdorferi sensu stricto, Borrelia garinii, and Borrelia afzelii, can cause the disease. This \*\*\*review\*\*\* will focus mainly on the pathophysiol. of Lyme arthritis, the long-term outcome of Lyme disease, and the recently licensed vaccine against Lyme disease.

RE.CNT 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 29 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 2002:150470 BIOSIS  
DN PREV200200150470  
TI Tick-borne disease: A \*\*\*review\*\*\* of the more common entities found in the northeastern United States.  
AU Coon, David (1); Versalovic, James  
CS (1) Department of Pathology, Massachusetts General Hospital, 55 Fruit Street, GRJ-2-245, Boston, MA, 02114: dcoon@partners.org, jamesv@bcm.tmc.edu USA  
SO Clinical Microbiology Newsletter, (January 15, 2002) Vol. 24, No. 2, pp. 9-14. print.  
ISSN: 0196-4399.  
DT General Review  
LA English

L13 ANSWER 4 OF 29 USPATFULL  
AN 2001:173362 USPATFULL  
TI Methods and compositions including a 13kD B. burgdorferi protein  
IN Sadziene, Ariadna, San Antonio, TX, United States  
Barbour, Alan G., San Antonio, TX, United States  
PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)  
PI US 6300101 B1 20011009  
AI US 1994-264036 19940622 (8)  
RLI Continuation-in-part of Ser. No. US 1993-79601, filed on 22 Jun 1993, now patented, Pat. No. US 5523089 Continuation of Ser. No. US 1992-924798, filed on 6 Aug 1992, now abandoned Continuation of Ser. No. US 1989-422881, filed on 18 Oct 1989, now abandoned  
PRAI DK 1988-5902 19881024  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Swartz, Rodney P.  
LREP Frommer Lawrence & Haug LLP, Kowalski, Thomas J.

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 1316

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB All \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\*

\*\*\*lato\*\*\* isolates characterized to date have one or a combination of several major outer surface proteins (Osp). Mutants of *B. burgdorferi* lacking Osp proteins were selected with polyclonal or monoclonal antibodies at a frequency of 10.sup.-6 to 10.sup.-5. One mutant that lacked OspA, B, C and D was further characterized in the present study. It was distinguished from the OspA.sup.+ B.sup.+ cells by its (i) auto-aggregation and slower growth rate, (ii) decreased plating efficiency on solid medium, (iii) serum- and complement-sensitivity, and (iv) diminished capacity to adhere to human umbilical vein endothelial cells. The Osp-less mutant was unable to evoke a detectable immune response after intradermal live cell immunization even though mutant survived in the skin the same duration as wild-type cells. Polyclonal mouse serum raised against Osp-less cells inhibited growth of the mutant but not of wild-type cells, an indication that other antigens are present on the surface of the Osp-less mutant. Two different classes, A and B, of monoclonal antibodies (mAb) with growth inhibiting properties for mutant cells were produced. Class A mAbs bound to 13 kDa surface proteins of *B. burgdorferi* sensu stricto and of *B. afzelii*. The minimum inhibitory concentration of the Fab fragment of one mAb of this class was 0.2 .mu.g/ml. Class B mAbs did not bind by Western Blot to *B. burgdorferi* cells but reacted with cells in an unfixed cell immunofluorescence assay and growth inhibition assay. These studies revealed hitherto unknown functional aspects of Osp proteins, notably serum-resistance, and indicated that in the absence of Osp proteins other antigens are expressed or become accessible at the cell's surface.

L13 ANSWER 5 OF 29 USPATFULL

AN 2001:167742 USPATFULL

TI Methods and compositions including a 13kDa *B. burgdorferi* protein

IN Sadziene, Ariadna, San Antonio, TX, United States

Barbour, Alan G., San Antonio, TX, United States

PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)

PI US 6296849 B1 20011002

AI US 1999-412060 19991004 (9)

RLI Division of Ser. No. US 1994-264036, filed on 22 Jun 1994

DT Utility

FS GRANTED

EXNAM Primary Examiner: Swartz, Rodney P.

LREP Frommer Lawrence & Haug, Kowalski, Thomas J.

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN 12 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 1332

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB All \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\*

\*\*\*lato\*\*\* isolates characterized to date have one or a combination of several major outer surface proteins (Osp). Mutants of *B. burgdorferi* lacking Osp proteins were selected with polyclonal or monoclonal

antibodies at a frequency of 10.sup.-6 to 10.sup.-5. One mutant that lacked OspA, B, C and D was further characterized in the present study. It was distinguished from the OspA.sup.+ B.sup.+ cells by its (i) auto-aggregation and slower growth rate, (ii) decreased plating efficiency on solid medium, (iii) serum- and complement-sensitivity, and (iv) diminished capacity to adhere to human umbilical vein endothelial cells. The Osp-less mutant was unable to evoke a detectable immune response after intradermal live cell immunization even though mutant survived in the skin the same duration as wild-type cells. Polyclonal mouse serum raised against Osp-less cells inhibited growth of the mutant but not of wild-type cells, an indication that other antigens are present on the surface of the Osp-less mutant. Two different classes, A and B, of monoclonal antibodies (mAb) with growth inhibiting properties for mutant cells were produced. Class A mAbs bound to 13 kDa surface proteins of *B. burgdorferi* sensu stricto and of *B. afzelii*. The minimum inhibitory concentration of the Fab fragment of one mAb of this class was 0.2 .mu.g/ml. Class B mAbs did not bind by Western blot to *B. burgdorferi* cells but reacted with cells in an unfixed cell immunofluorescence assay and growth inhibition assay. These studies revealed hitherto unknown functional aspects of Osp proteins, notably serum-resistance, and indicated that in the absence of Osp proteins other antigens are expressed or become accessible at the cell's surface.

L13 ANSWER 6 OF 29 USPATFULL

AN 2001:93350 USPATFULL

TI Chromosomally-encoded membrane protein of *borrelia burgdorferi*

IN Aron, Lieselotte, Hartsdale, NY, United States  
Cabello, Felipe, Hartsdale, NY, United States  
Godfrey, Henry P., Scarsdale, NY, United States  
Schwartz, Ira, Spring Valley, NY, United States

PA New York Medical College, Valhalla, NY, United States (U.S. corporation)

PI US 6248583 B1 20010619

AI US 1994-313412 19940927 (8)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Allen, Marianne P.

LREP Nixon Peabody LLP

CLMN Number of Claims: 8

ECL Exemplary Claim: 1

DRWN 4 Drawing Figure(s); 4 Drawing Page(s)

LN.CNT 1285

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to an isolated membrane protein or polypeptide encoded by chromosomal DNA of *Borrelia burgdorferi* (e.g., BmpC). This protein is encoded by a DNA molecule (e.g., bmpC) and is useful in vaccines to prevent infection by *Borrelia burgdorferi*, while antibodies raised against this protein can be employed in passively immunizing those already infected by the organism. Both these proteins and antibodies may be utilized in diagnostic assays to detect *Borrelia burgdorferi* and immune response in tissue or body fluids. Likewise, the DNA molecule can be used for detection of this organism.

L13 ANSWER 7 OF 29 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2

AN 2001:706287 CAPLUS

TI Successful vaccination for lyme disease: A novel mechanism?

AU Exner, Maurice  
CS Quest Diagnostics' Nichols Institute, San Juan Capistrano, CA, 92673, USA  
SO Expert Opin. Biol. Ther. (2001), 1(5), 783-793  
CODEN: EOBTA2; ISSN: 1471-2598

PB Ashley Publications Ltd.

DT Journal

LA English

AB \*\*\**Borrelia*\*\*\* \*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\* \*\*\**lato*\*\*\* is the etiologic agent of Lyme disease, which is a multi-system disorder resulting from the transmission of organisms from an infected tick. According to the US Centers for Disease Control, the incidence of Lyme disease in the US has increased 25-fold since national surveillance began and the geog. spread of Lyme disease causing spirochetes would indicate that the annual no. of cases will continue to rise. Humoral immunity has been shown to play a role in protection and this has spurred efforts towards developing a Lyme disease vaccine. A no. of protective immunogens have been characterised to date, but due to the heterogeneity of Lyme disease Borreliae, no single mol. has proven to be completely effective as a vaccine. This \*\*\*review\*\*\* will describe the immunogens that have been used to protect against *B. burgdorferi* infection, with a focus on the inherent challenges involved with providing successful immunity to *B. burgdorferi*. In addn., the promising aspects and the limitations of each protective immunogen will be discussed.

RE.CNT 118 THERE ARE 118 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 29 CABO COPYRIGHT 2002 CABO DUPLICATE 3

AN 2002:31047 CABO

DN 20013172826

TI Lyme borreliosis in the UK - ecology and risks to domestic animals and man

AU Cutler, S. J.; Woodward, M. J.

CS Veterinary Laboratories Agency, New Haw, Addlestone, Surrey, KT15 3NB, UK.

SO Reviews in Medical Microbiology, (2001) Vol. 12, No. 4, pp. 199-209. 57 ref.

ISSN: 0954-139X

DT Journal

LA English

AB This \*\*\*review\*\*\* discusses the interactions of different genospecies of Lyme borreliosis spirochaetes ( \*\*\**Borrelia*\*\*\* \*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\* \*\*\**lato*\*\*\* ), as well as their differing tick vectors (*Ixodes ricinus*), vertebrate reservoirs (rodents, rabbits, hedgehogs, birds, dogs, sheep, goats) and 'accidental hosts' (cattle, horses, and deer). Particular reference is made to spirochaete-host interactions and occurrence of pathological consequences. The unique prevalence of enzoonotic cycles in UK is emphasized. Risk factors for acquiring Lyme borreliosis in man are discussed.

L13 ANSWER 9 OF 29 CAPLUS COPYRIGHT 2002 ACS

AN 2001:621572 CAPLUS

DN 135:285414

TI Adhesion mechanisms of the Lyme disease spirochete, *Borrelia burgdorferi*

AU Coburn, Jenifer

CS Division of Rheumatology and Immunology, Tufts-New England Medical Center, Boston, MA, 02111, USA

SO Curr. Drug Targets: Infect. Disord. (2001), 1(2), 171-179

CODEN: CDTIAS; ISSN: 1568-0053  
PB Bentham Science Publishers Ltd.  
DT Journal; General Review  
LA English  
AB A \*\*\*review\*\*\* with 67 refs. \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\*  
( \*\*\*sensu\*\*\* \*\*\*lato\*\*\* ), the spirochete that causes Lyme disease, is among the most fascinating and enigmatic of bacterial pathogens. An obligate parasite of other organisms, *B. burgdorferi* is maintained in the mammalian reservoir (small rodents) by tick-mediated transmission from infected individuals to other members of the population. The complex requirements that must be met to ensure survival in an immunocompetent rodent and in the tick vector, coupled with a relatively small genome, suggest that *B. burgdorferi* has evolved elegant strategies for interacting with its hosts. Among these strategies are several distinct mechanisms of adhesion to mammalian cells and extracellular matrix components. The mammalian receptors for *B. burgdorferi* that have been most thoroughly studied, and for which candidate bacterial ligands have been identified, are decorin, fibronectin, glycosaminoglycans, and .beta.3-chain integrins.

RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 2001110933 EMBASE

TI Lyme disease in central Europe.

AU Hercogova J.; Brzonna I.

CS J. Hercogova, Department of Dermatology, Charles University, Motol University Hospital, V Uvalu 84, 150 06 Prague, Czech Republic.  
jana.hercogova@lfmotol.cuni.cz

SO Current Opinion in Infectious Diseases, (2001) 14/2 (133-137).

Refs: 42

ISSN: 0951-7375 CODEN: COIDES

CY United Kingdom

DT Journal; General Review

FS 004 Microbiology

013 Dermatology and Venereology

017 Public Health, Social Medicine and Epidemiology

026 Immunology, Serology and Transplantation

037 Drug Literature Index

LA English

SL English

AB Lyme borreliosis is a fascinating disease, the aetiopathology of which is not yet completely known. Different subspecies of \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\* are responsible for the variable clinical course of the disease. Some new cutaneous (alopecia) and ocular (photophobia and retinal vasculitis) manifestations have been described and the largest prospective study on erythema migrans during pregnancy was published during the last year. Optimal therapy of Lyme borreliosis is still lacking, but doxycycline, amoxicillin, penicillin, and ceftriaxone are recommended most frequently. .COPYRGT. 2001 Lippincott Williams & Wilkins.

L13 ANSWER 11 OF 29 CABA COPYRIGHT 2002 CAB

AN 2001:136145 CABA

DN 20013131032

TI Taxonomy of \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\*

\*\*\*lato\*\*\* - interest in clinic and epidemiology  
AU Postic, D.; Baranton, G.; Grce, M. [EDITOR]; Pigac, J. [EDITOR]; Mrsa, V. [EDITOR]  
CS Unite de Bacteriologie Moleculaire et Medicale, Institut Pasteur, 28, Rue du Dr. Roux, 75724 Paris Cedex 15, France.  
SO Periodicum Biologorum, (2001) Vol. 103, No. 2, pp. 97-102. 50 ref.  
Meeting Info.: Second Croatian Congress of Microbiology, Brijuni Islands, Croatia, October, 2000.  
ISSN: 0031-5362  
DT Journal; Conference Article  
LA English  
AB A \*\*\*review\*\*\* on the epidemiology, genetic diversity and taxonomy of *B. burgdorferi* sensu lato, as well as species within the *B. burgdorferi* sensu lato complex (*B. garinii*, *B. burgdorferi* sensu stricto and *B. afzelii*) is presented. The clinical features of infections by these organisms are discussed.

L13 ANSWER 12 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 2000263684 EMBASE

TI The wild hidden face of Lyme borreliosis in Europe.

AU Humair P.-F.; Gern L.

CS L. Gern, Institut de Zoologie, Departement de Parasitologie, Rue Emile-Argand 11, 2007 Neuchatel 7, Switzerland

SO Microbes and Infection, (2000) 2/8 (915-922).

Refs: 54

ISSN: 1286-4579 CODEN: MCINFS

CY France

DT Journal; General Review

FS 004 Microbiology

017 Public Health, Social Medicine and Epidemiology

LA English

SL English

AB Lyme borreliosis is a zoonosis affecting humans in the Northern hemisphere. The pathogen, \*\*\**Borrelia*\*\*\* \*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\* \*\*\**lato*\*\*\* (sl), persists in endemic areas through a maintenance cycle involving ticks and wild animals. The description of different genospecies associated with Lyme borreliosis in Europe has generated the question concerning the maintenance of these pathogens in nature: how do closely related bacterial species like *B. burgdorferi* sl circulate between one main tick species, *Ixodes ricinus*, and several vertebrate host species? Recent studies have provided evidence that specific associations exist in some areas between *Borrelia* species and vertebrate hosts. The present paper based on this recent knowledge discusses various aspects of the ecology of the disease in Western Europe, in particular the maintenance and dispersal of the pathogens, and brings up some interesting questions. (C) 2000 Editions scientifiques et medicales Elsevier SAS.

L13 ANSWER 13 OF 29 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4

AN 1999:710532 CAPLUS

DN 132:75717

TI Molecular typing of \*\*\**Borrelia*\*\*\* \*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\* \*\*\**lato*\*\*\* : taxonomic, epidemiological, and clinical implications

AU Wang, Guiqing; Van Dam, Alje P.; Schwartz, Ira; Dankert, Jacob

CS Department of Medical Microbiology, Academic Medical Centre, University of

Amsterdam, Amsterdam, 1105 AZ, Neth.  
SO Clin. Microbiol. Rev. (1999), 12(4), 633-653  
CODEN: CMIREX; ISSN: 0893-8512  
—QR 67.CS6  
PB American Society for Microbiology  
DT Journal; General Review  
LA English  
AB A \*\*\*review\*\*\* with 292 refs. \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\*  
\*\*\*sensu\*\*\* \*\*\*lato\*\*\*, the spirochete that causes human Lyme  
borreliosis (LB), is a genetically and phenotypically divergent species.  
In the past several years, various mol. approaches have been developed and  
used to det. the phenotypic and genetic heterogeneity within the  
LB-related spirochetes and their potential assocn. with distinct clin.  
syndromes. These methods include serotyping, multilocus enzyme  
electrophoresis, DNA-DNA reassocn. anal., rRNA gene restriction anal.  
(ribotyping), pulsed-field gel electrophoresis, plasmid fingerprinting,  
randomly amplified polymorphic DNA fingerprinting anal., species-specific  
PCR and PCR-based restriction fragment length polymorphism (RFLP) anal.,  
and sequence anal. of 16S rRNA and other conserved genes. On the basis of  
DNA-DNA reassocn. anal., 10 different Borrelia species have been described  
within the *B. burgdorferi* sensu lato complex: *B. burgdorferi* sensu  
stricto, *Borrelia garinii*, *Borrelia afzelii*, *Borrelia japonica*, *Borrelia*  
*andersonii*, *Borrelia valaisiana*, *Borrelia lusitaniae*, *Borrelia tanukii*,  
*Borrelia turdi*, and *Borrelia bissettii* sp. nov. To date, only *B.*  
*burgdorferi* sensu stricto, *B. garinii*, and *B. afzelii* are well known to be  
responsible for causing human disease. Different *Borrelia* species have  
been assoccd. with distinct clin. manifestations of LB. In addn., *Borrelia*  
species are differentially distributed worldwide and may be maintained  
through different transmission cycles in nature. In this paper, the mol.  
methods used for typing of *B. burgdorferi* sensu lato are reviewed. The  
current taxonomic status of *B. burgdorferi* sensu lato and its epidemiol.  
and clin. implications, esp. correlation between the variable clin.  
presentations and the infecting *Borrelia* species, are discussed in detail.

RE.CNT 292 THERE ARE 292 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 14 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 1999052159 EMBASE

TI Genospecies and their influence on immunoblot results.

AU Wilske B.; Hauser U.; Lehnert G.; Jauris-Heipke S.

CS Dr. B. Wilske, M.v. Pettenkofer-Inst. Hyg/Med Mikr., Lehrstuhl  
Bakteriologie, Pettenkoferstrasse 9a, D-80336 Munchen, Germany

SO Wiener Klinische Wochenschrift, (23 Dec 1998) 110/24 (882-885).

Refs: 20

ISSN: 0043-5325 CODEN: WKWOAO

CY Austria

DT Journal; General Review

FS 004 Microbiology

LA English

SL English

AB In Europe at least three human pathogenic species of \*\*\*Borrelia\*\*\*  
\*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\* are the causative  
agents of Lyme borreliosis. All three species have been isolated or  
detected by PCR from skin, CSF and synovial fluid of patients with skin  
lesions, neuroborreliosis and Lyme arthritis respectively. Studies using  
strains representing the three species as antigen for the immunoblot

revealed that interpretation criteria depend strictly on the strain used as antigen. More than using certain species as antigen it is important to use strains (f.e. *B. afzelii* strain PKo) expressing certain immuno-dominant antigens like OspC and p17 which may not be expressed by other strains *in vitro*. Using strain PKo as antigen the two band criterium can be used without loss of too much sensitivity compared to using *B. burgdorferi* sensu stricto strain PKa2 and *B. garinii* strain PBi. The use of recombinant antigens allows selection of highly specific and combination of homologous antigens from different strains; however not all desirable antigens have been recombinantly expressed. Addition of p17 and p58 as antigens may improve the sensitivity of the hitherto described recombinant antigen immunoblots containing the antigens p83/100, p39, OspC and the p41 internal fragment.

L13 ANSWER 15 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 1999052153 EMBASE

TI Natural history of \*\*\**Borrelia*\*\*\* \*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\*  
\*\*\**lato*\*\*\*

AU Gern L.; Humair P.-F.

CS Dr. L. Gern, Institut de Zoologie, Emile Argand 11, CH-2000 Neuchatel,  
Switzerland

SO Wiener Klinische Wochenschrift, (23 Dec 1998) 110/24 (856-858).

Refs: 23

ISSN: 0043-5325 CODEN: WKWOAO

CY Austria

DT Journal; General Review

FS 004 Microbiology

LA English

SL English

AB Lyme borreliosis is a zoonosis: its causative agent, *B. burgdorferi*, circulates between ticks and a large range of vertebrates. Identification of the hosts which are responsible for the infection of the vectors is extremely important to determine the potential risk of infection in an habitat. Various small mammals and bird species are considered reservoirs for the Lyme disease spirochetes. Grey and red squirrels, hedgehogs as well as hares and rabbits can develop an infection and transmit *B. burgdorferi* sensu lato to feeding ticks. In Eurasian endemic areas, many different *Borrelia* species circulate between ticks and vertebrate hosts. Studies have shown that European and Asian genospecies are associated with specific groups of vertebrate hosts, such as *B. valaisiana* and *B. garinii* with birds, *B. afzelii* with small mammals and *B. burgdorferi* ss and *B. afzelii* with red squirrels. However, such associations are not always observed as in Japan where *B. garinii*, *B. afzelii* and unidentified *Borrelia* species are found in small mammals. Some enzootic cycles involving tick species which do not feed at all humans or which rarely feed on humans have been described in Europe and USA. It is likely that many existing enzootic foci have yet to be discovered. The circulation of *B. burgdorferi* in silent foci does not have important implications for human health, but it demonstrates the complexity of the ecology of this microorganism and the variety of ecological niches this spirochete can occupy.

L13 ANSWER 16 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 1999052152 EMBASE

TI Molecular epidemiology of the aetiological agents of Lyme borreliosis.

AU Baranton G.; Ras N.M.; Postic D.  
CS Dr. G. Baranton, Unite de Bacteriol. Molec./Medicale, Institut Pasteur, 28  
rue du Docteur Roux, F-75724 Paris Cedex 15, France  
SO Wiener Klinische Wochenschrift, (23 Dec 1998) 110/24 (850-855).

Refs: 38  
ISSN: 0043-5325 CODEN: WKWOAO

CY Austria  
DT Journal; General Review  
FS 004 Microbiology  
006 Internal Medicine

LA English  
SL English; German

AB Ten species are up to now recognized among \*\*\**Borrelia*\*\*\*  
\*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\* \*\*\**lato*\*\*\* complex. Among those,  
only three (*Borrelia burgdorferi sensu stricto*, *B. garinii* and *B. afzelii*)  
are reported to be pathogenic for humans and each responsible for a  
predominant clinical form of Lyme borreliosis. Each species is  
characterized by its vectors (Ixodidae), its host spectrum, its  
organotropism (for the pathogenic ones) and its geographical repartition.  
*Borrelia* are strictly parasitic and essentially clonal bacteria. Our goal  
was to explore the diversity of this bacterial complex. We selected, by  
several molecular markers, atypical isolates and compared them to already  
known species representative strains by RFLP or sequencing. The results  
show an unexpected diversity at a level which could be a species one  
leading to the conclusion that the structure of the \*\*\**Borrelia*\*\*\*  
\*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\* \*\*\**lato*\*\*\* complex is a high  
number of small (by their populations) clones among which emerge some  
large ones usually corresponding to the pathogenic species. Our data also  
allow to speculate on when, where and how these species evolved and  
migrated.

L13 ANSWER 17 OF 29 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

5

AN 1999:7364 BIOSIS  
DN PREV199900007364  
TI Lyme disease in Italy, 1983-1996.  
AU Ciceroni, L.; Ciarrocchi, S.  
CS Dep. Bacteriol. Med. Mycol., Ist. Superiore Sanita, Viale Regina Elena  
299, 00161 Rome Italy  
SO Microbiologica (Pavia), (Oct., 1998) Vol. 21, No. 4, pp. 407-418.

ISSN: 1121-7138.  
DT General Review  
LA English

AB This paper is a brief \*\*\*review\*\*\* of the epidemiology of Lyme disease  
in Italy. The first case of the illness was identified by Crovato in  
Liguria in 1983. In the following years, many other cases have been  
reported from all Italian regions with the exception of Valle d'Aosta,  
Basilicata and Calabria. The exact number of cases in our country is not  
known because Lyme disease was not a notifiable disease until 1990, but on  
the basis of literature data, at least 1324 cases have been observed in  
the fourteen-year period 1983-1996. Friuli-Venezia Giulia, Veneto and  
Trentino-Alto Adige are the main regions involved. Only few cases of  
illness have been described in Mid and Southern Italy and in the Islands  
(6.0%). No reports exist on Lyme disease in animals. There is, however,  
serological evidence of infection of domestic and wild animals. The

causative agent, \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\*, was first isolated from Ixodes ricinus ticks by Cinco in Trieste in 1977. Since then many other strains, belonging to three different genomic species (B. burgdorferi sensu stricto, B. garinii and B. afzelii), have been isolated from humans, reservoir hosts and ticks. Cases were reported for all age-groups, more frequently in females, following the typical seasonal course, with a marked seasonality from spring to autumn, when ticks are more active. Erythema chronicum migrans was the most frequent manifestation of LD. Several studies have been conducted on groups at risk (forest workers, gamekeepers, etc.). In contrast to the high prevalence of antibodies to B. burgdorferi sensu lato in the groups at risk (up to 27.2% for forest workers), the seroprevalence of the healthy population is, in general, lower.

L13 ANSWER 18 OF 29 CABA COPYRIGHT 2002 CABI DUPLICATE 6

AN 1999:25323 CABA

DN 990500609

TI Lyme borreliosis (Lyme disease): interactions of \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\* with human (and other mammalian) hosts

AU Sigal, L. H.

CS Division of Rheumatology and Connective Tissue Research, Lyme Disease Center, UMDNJ-Robert Wood Johnson Medical School, 1 Robert Wood Johnson Place MEB 484, New Brunswick, NJ 08903-0019, USA.

SO Bulletin de l'Institut Pasteur, (1998) Vol. 96, No. 3, pp. 189-206. 228 ref.

DT Journal

LA English

SL French

AB In the 20 years since its description, Lyme disease has evolved from being a curiosity in 3 small communities on the east bank of the Connecticut River to the most common vector-borne disease in the USA and Germany, and a worldwide concern. In this short time, the aetiologic agent has been identified and grown, the clinical syndromes due to this agent have been delineated, seroconfirmatory tests developed, effective therapeutic regimens determined, a vaccine found to be safe and effective, and the epidemiology and ecology understood sufficiently to establish avoidance and prevention strategies. However, the mechanisms whereby the aetiologic agent, B. burgdorferi s. l. actually causes tissue damage/dysfunction remain to be defined. The following represents a \*\*\*review\*\*\* of some proposed immunopathogenic mechanisms with a focus on possible autoimmunity.

L13 ANSWER 19 OF 29 CABA COPYRIGHT 2002 CABI

AN 1998:63960 CABA

DN 980502135

TI Prevalence rates of \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\* in host-seeking Ixodes ricinus ticks in Europe

AU Hubalek, Z.; Halouzka, J.

CS Institute of Landscape Ecology, Academy of Sciences of the Czech Republic, Klasterni 2, Czech Republic.

SO Parasitology Research, (1998) Vol. 84, No. 3, pp. 167-172. 75 ref.

ISSN: 0044-3255

DT Journal

LA English

AB *Borrelia burgdorferi* s.l. spirochaetes have been found in all examined *I. ricinus* populations in Europe. Based on a \*\*\*review\*\*\* of published and unpublished information from 23 countries, the overall mean proportions of unfed *I. ricinus* infected with *B. burgdorferi* s.l. were 1.9% (range 0-11%), 10.8% (2-43%) and 17.4% (3-58%) for larvae (n = 5699), nymphs (n = 48 804) and adults (n = 41 666), respectively. However, the results varied according to the method used. Cultivation in BSK medium is the least sensitive technique (an average of 11% of adult ticks found infected), whereas polymerase chain reaction detecting spirochaetal DNA is probably the most sensitive method (29% of adults found infected). Microscopic methods (dark field, phase contrast, direct or indirect fluorescence) are generally comparable to each other (17-20% of adults found infected) and should be regarded as standard procedures because they also make possible a quantitative estimation of spirochaetes in the vector. Some technical problems of these methods are discussed.

L13 ANSWER 20 OF 29 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

7

AN 1998:172213 BIOSIS

DN PREV199800172213

TI Distribution of \*\*\**Borrelia*\*\*\* \*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\* \*\*\**lato*\*\*\* genomic groups in Europe, a \*\*\*review\*\*\* .

AU Hubalek, Z. (1); Halouzka, J.

CS (1) Inst. Landscape Ecol., Acad. Sci., Klasterni 2, CZ-69142 Valtice Czech Republic

SO European Journal of Epidemiology, (Dec., 1997) Vol. 13, No. 8, pp. 951-957.

ISSN: 0393-2990.

DT General Review

LA English

AB The survey is based on a total of 1263 records (738 isolations and 525 molecular DNA detections) of five *Borrelia burgdorferi* s.l. genomic groups available from 26 European countries: *B. burgdorferi* sensu stricto, *B. afzelii*, *B. garinii*, *B. valaisiana* (= VS116) and *B. lusitaniae* (= PoTiB2). It shows the geographic distribution, the source (ixodid ticks 802 records, fleas 2 records, mosquitoes 2 records, wild mammals 66 records, human patients 391 records) and the association of the genomic groups with particular clinical manifestations of Lyme borreliosis in humans (*B. afzelii* significantly prevails in skin lesions whereas *B. garinii* is more often associated with neuroborreliosis). The most frequent genomic groups in Europe are *B. garinii* (501 records) and *B. afzelii* (469 records). They occur across the continent and islands, whereas the third frequent genomic group, *B. burgdorferi* s.s. (201 records), has only rarely been isolated in eastern Europe. The remaining genomic groups, i.e. *B. valaisiana* (85 records) and *B. lusitaniae* (7 records) have only been isolated from, or detected in, *Ixodes ricinus* ticks in a few European countries.

L13 ANSWER 21 OF 29 LIFESCI COPYRIGHT 2002 CSA

AN 1998:64766 LIFESCI

TI Distribution of \*\*\**Borrelia*\*\*\* \*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\* \*\*\**lato*\*\*\* genomic groups in Europe, a \*\*\*review\*\*\* .

AU Hubalek, Z.; Halouzka, J.

CS Inst. Landscape Ecol., Acad. Sci., Klasterni 2, CZ-69142 Valtice, Czech Rep.

SO EUR. J. EPIDEMIOL., (1997) vol. 13, no. 8, pp. 851-957.

ISSN: 0393-2990.  
DT Journal  
FS J  
LA English  
SL English  
AB The survey is based on a total of 1263 records (738 isolations and 525 molecular DNA detections) of five *Borrelia burgdorferi* s.l. genomic groups available from 26 European countries: *B. burgdorferi*, *sensu stricto*, *B. afzelii*, *B. garinii*, *B. valaisiana* (= VS116) and *B. lusitaniae* (= PoTiB2). It shows the geographic distribution, the source (ixodid ticks 802 records, fleas 2 records, mosquitoes 2 records, wild mammals 66 records, human patients 391 records) and the association of the genomic groups with particular clinical manifestations of Lyme borreliosis in humans (*B. afzelii* significantly prevails in skin lesions whereas *B. garinii* is more often associated with neuroborreliosis). The most frequent genomic groups in Europe are *B. garinii* (501 records) and *B. afzelii* (469 records). They occur across the continent and islands, whereas the third frequent genomic group, *B. burgdorferi* s.s. (201 records), has only rarely been isolated in eastern Europe. The remaining genomic groups, i.e. *B. valaisiana* (85 records) and *B. lusitaniae* (7 records) have only been isolated from, or detected in, *Ixodes ricinus* ticks in a few European countries.

L13 ANSWER 22 OF 29 CAPLUS COPYRIGHT 2002 ACS  
AN 1997:426866 CAPLUS  
DN 127:119348  
TI Present status of Lyme borreliosis and characterization of Lyme disease  
    *Borrelia* isolated in Japan  
AU Masuzawa, Toshiyuki  
CS School Pharamaceutical Sciences, University Shizuoka, Shizuoka, 422, Japan  
SO Yakugaku Zasshi (1997), 117(6), 319-338  
    CODEN: YKKZAJ; ISSN: 0031-6903  
PB Pharmaceutical Society of Japan  
DT Journal; General Review  
LA Japanese  
AB A \*\*\*review\*\*\* with 59 refs. Lyme disease is a multisystemic disorder cause by infection with \*\*\**Borrelia*\*\*\* \*\*\**burgdorferi*\*\*\* \*\*\**sensu*\*\*\* \*\*\**lato*\*\*\* which is carried by ticks of the *Ixodes ricinus* complex. The agent was discovered in 1982 in North America and the disease is recognized as an emerging infectious diseases in North America and Europe. Japanese *Borrelia* isolates were characterized by genetic and immunol. anal. Isolates from *Ixodes ovatus* were found to be unique by DNA/DNA hybridization anal., restriction fragment length polymorphism analyze of the flagellin gene and the 16S rRNA genes, and were described as new species, *Borrelia japonica*. Isolates from *Ixodes persulcatus* were detd. as *Borrelia garinii* and *Borrelia afzelii*. However, *B. garinii* found in Japan was different from those from Europe in immunol. and genetic characteristics of outer surface protein A, but *B. afzelii* isolates from Japan and Europe were identical. An exptl. model of arthritis related to Lyme disease using outbred ddY mice was established. Whole cell vaccine prep'd. from North American and European isolates could not elicit protective immunity against infection of Japanese isolates. This implies that vaccine development using Japanese isolates is necessary. *Borrelia* bound specifically to galactosylceramide (GalCer), glucosylceramide and lactosylceramide which are present in various types of cells as binding receptor, but not to other glycosphingolipids.

Furthermore, the infectivity of Borrelia may be assoccd. with the binding to glycosphingolipids on the cell surface and a 67 kDa protein of Lyme disease Borrelia may be involved in binding of Borrelia to GalCer.

L13 ANSWER 23 OF 29 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

8

AN 1997:440234 BIOSIS

DN PREV199799739437

TI Clinical findings for patients with Lyme borreliosis caused by \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\* with genotypic and phenotypic similarities to strain 25015.

AU Strle, Franc; Picken, Roger N.; Cheng, Yu; Cimperman, Jozef; Maraspin, Vera; Lotric-Furlan, Stanka; Ruzic-Sabljic, Eva; Picken, Maria M. (1)

CS (1) Dep. Pathol., Room 2242, Build. 110, Loyola Univ. Med. Center, 2160 South First Ave., Maywood, IL 60153 USA

SO Clinical Infectious Diseases, (1997) Vol. 25, No. 2, pp. 273-280.  
ISSN: 1058-4838.

DT (CASE STUDY)

LA English

AB In the course of performing culture isolation of \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\* for the diagnosis of Lyme borreliosis in Slovenia, we encountered nine patients who were infected with atypical strains. Molecular analyses of these strains suggested that they were more closely related to the North American tick isolate, strain 25015 (which belongs to the DN127 genomic group of *B. burgdorferi* sensu lato), than they were to the three species (*B. burgdorferi* sensu stricto, *Borrelia garinii*, and *Borrelia afzelii*) hitherto found to be associated with European Lyme borreliosis. \*\*\*Review\*\*\* of the case histories of these patients revealed some atypical clinical features and variability in clinical presentation. In this study, we present the clinical findings for these patients and discuss their significance for the diagnosis of Lyme borreliosis. The DN127 genomic group shares with *B. burgdorferi* sensu stricto the distinction of being present in both the Old and New Worlds.

L13 ANSWER 24 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 97153115 EMBASE

DN 1997153115

TI Microbiology of *Borrelia burgdorferi*.

AU Rosa P.A.

CS Dr. P.A. Rosa, Microbial Structure/Function Lab., Rocky Mountain Laboratories of NIAID, NIH, 903 South Fourth Street, Hamilton, MT 59840, United States

SO Seminars in Neurology, (1997) 17/1 (5-10).

Refs: 83

ISSN: 0271-8235 CODEN: SEMNEP

CY United States

DT Journal; General Review

FS 004 Microbiology

008 Neurology and Neurosurgery

LA English

SL English

AB This article reviews the natural history, taxonomy, physical structure, growth requirements, and molecular structure of \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\*, the causative agent of

Lyme disease. These spirochetal bacteria are maintained in nature through an infectious cycle between wild mammals and ticks. Borreliae are fastidious, slow-growing bacteria, found only in association with their arthropod or mammalian hosts in nature, and propagatable in the laboratory in a rich growth medium. The characteristic shape of borreliae is imposed by periplasmic flagella, located beneath the outer membrane and attached to the protoplasmic cylinder. The outer membrane of borreliae contains a number of abundant lipoproteins that are of serodiagnostic utility and currently under consideration as vaccine targets. The borrelial genome is unique in structure, organization, and copy number. Recent experiments demonstrate the feasibility of specific gene inactivation as a means with which to study the biology of borreliae and the pathogenesis of Lyme disease.

L13 ANSWER 25 OF 29 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

9

AN 1996:543571 BIOSIS

DN PREV199699265927

TI Prevalence of serum antibodies to \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\* and Ehrlichia sp. among dogs in the coastal part of Aust-Agder, Norway.

AU Akerstedt, Johan (1); Blakstad, Ellef; Artursson, Karin

CS (1) Veterinaerinst., Postboks 8156 Dep., 0033 Oslo Norway

SO Norsk Veterinaertidsskrift; (1996) Vol. 108, No. 8-9, pp. 537-543.

ISSN: 0332-5741.

DT Article

LA Norwegian

SL Norwegian; English

AB Lyme borreliosis is a tick-borne disease, caused by spirochetes belonging to the \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\* complex. Granulocytic ehrlichiosis is presumably also tick-borne and is in dogs caused by the rickettsia Ehrlichia sp. The aim of the present study was to estimate antibody titers against Borrelia burgdorferi s. l. and Ehrlichia sp. with the immune fluorescence antibody test (IFA). In all, 87 dogs from the coastal area of Aust-Agder county, endemic for the tick *Ixodes ricinus*, were sampled. Both dogs with and without signs of clinical disease were included in the study, but none of the animals had obvious clinical signs of tick-borne disease. Twelve (13.8%) of the dogs had antibody titers to *B. afzelii*, and 20 (23.0%) had antibody titers to *E. equi*. A statistically significant correlation was found between seropositivity for Ehrlichia sp. and urogenital disorders. It is concluded that *B. burgdorferi* s. l. and Ehrlichia sp. may infect dogs in Norway and a \*\*\*review\*\*\* of the diseases and the involved vectors is given, with special emphasis on diagnosis.

L13 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2002 ACS

AN 1996:351318 CAPLUS

DN 125:31534

TI Immunological and molecular variability of OspA and OspC. Implications for Borrelia vaccine development

AU Wilske, B.; Busch, U.; Fingerle, V.; Jauris-Heipke, S.; Preac Mursic, V.; Roessler, D.; Will, G.

CS Max-von-Pettenkofer Institut fur Hygiene and Medizinische Mikrobiologie, Munich, D-80336, Germany

SO Infection (Munich) (1996), 24(2), 208-212

CODEN: IFTNAL; ISSN: 0300-8126  
DT Journal; General Review  
LA English  
AB A \*\*\*review\*\*\* with 32 refs. \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\*  
\*\*\*sensu\*\*\* \*\*\*lato\*\*\*, the etiol. agent of Lyme borreliosis, is  
considerably heterogeneous in Europe. Since the outer surface proteins  
OspA and OspC are the most promising candidates for a Borrelia vaccine,  
the immunol. heterogeneity of these proteins was investigated. By  
immunol. anal. with monoclonal antibodies and sequence anal. of PCR  
amplified OspA and OspC at least seven and 16 different types, resp., were  
found. Whereas skin isolates (n=68) were quite homogeneous (84% belonged  
to OspA-serotype 2 or Borrelia afzelii), isolates from human cerebrospinal  
fluid and from ticks (n=43 and n=90 resp.) were highly heterogeneous in  
their OspA-serotypes with prevalence of the Borrelia garinii assocd. types  
(about 70%). OspA-type 4 was often found among isolates from  
cerebrospinal fluid (28%). In ticks type 4 OspA has not been detected by  
culture so far. However, as reported in a previous study, type 4 OspA  
could be detected in ticks by the highly sensitive PCR technique.

L13 ANSWER 27 OF 29 CAPLUS COPYRIGHT 2002 ACS

AN 1995:692990 CAPLUS

DN 123:333935

TI Laboratory diagnosis of \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\*  
\*\*\*sensu\*\*\* \*\*\*lato\*\*\* infections

AU Putzker, Michael; Sauer, Henner

CS Hyg. Inst., Siegen, Germany

SO Klin. Labor (1995), 41(6), 431-9

CODEN: KLLAEA; ISSN: 0941-2131

DT Journal; General Review

LA German

AB A \*\*\*review\*\*\* with 57 refs. on the supplementation of the clin.  
diagnosis of Lyme borreliosis by serolog. lab. tests, including indirect  
hemagglutination test, EIA, IFA, and IB.

L13 ANSWER 28 OF 29 CAPLUS COPYRIGHT 2002 ACS

AN 1994:600446 CAPLUS

DN 121:200446

TI Molecular biology of the Borrelia, bacteria with linear replicons

AU Girons, I. Saint; Old, I. G.; Davidson, B. E.

CS Unit Bacteriologie Moleculaire Medicale, Institute Pasteur, Paris, 75724,  
Fr.

SO Microbiology (Reading, U. K.) (1994), 140(8), 1803-16

CODEN: MROBEO; ISSN: 1350-0872

DT Journal; General Review

LA English

AB A \*\*\*review\*\*\*, with .aprx.100 refs., giving focus to the mol. biol.  
of the causative agents of Lyme disease and North American relapsing fever  
( \*\*\*Borrelia\*\*\* \*\*\*burgdorferi\*\*\* \*\*\*sensu\*\*\* \*\*\*lato\*\*\*  
and Borrelia hermsii, resp.). Topics include (1) the Borrelia genome, (2)  
major outer-membrane proteins of Borrelia, (3) endoflagella of  
spirochaetes, (4) potential involvement of heat-shock proteins to  
autoimmune reactions, and (5) genetic transfer and genetic tools.

L13 ANSWER 29 OF 29 LIFESCI COPYRIGHT 2002 CSA

AN 95:42207 LIFESCI

QR1.J4

TI Molecular biology of the Borrelia, bacteria with linear replicons  
AU Saint-Girons, I.; Old, I.G.; Davidson, B.E.  
CS Unite Bacteriol. Mol. Med., Inst. Pasteur, 75724 Paris Cedex 15, France  
SO MICROBIOLOGY, (1994) vol. 140, no. 8, pp. 1803-1816.  
ISSN: 0001-8769.

DT Journal  
TC General Review  
FS J; G  
LA English

AB Interest in Borrelia increased dramatically after the recent discovery of Lyme disease and the observation that it is caused by a novel member of the genus. Borrelia are spirochaetes, organisms that comprise a separate phylum in the kingdom of eubacteria. They differ from other bacteria in having a helical shape with multiple waves and endoflagella. In this \*\*\*review\*\*\*, we concentrate on the molecular biology of the causative agents of Lyme disease and North American relapsing fever (\*\*\*Borrelia\*\*\*, \*\*\*burgdorferi\*\*\*, \*\*\*sensu\*\*\*, \*\*\*lato\*\*\* and Borrelia hermsii, respectively) because they have received the most research attention. To contain the \*\*\*review\*\*\* within reasonable limits we have not attempted to cover the taxonomy of the Borrelia or the widespread literature on antigenic variation of B. hermsii.

=> s l3 and garinii and ip90  
L14 44 L3 AND GARINII AND IP90

=> dup rem l14  
PROCESSING COMPLETED FOR L14  
L15 21 DUP REM L14 (23 DUPLICATES REMOVED)

=> d bib ab kwic 1-  
YOU HAVE REQUESTED DATA FROM 21 ANSWERS - CONTINUE? Y/(N):y

L15 ANSWER 1 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE  
1  
AN 2001:422724 BIOSIS  
DN PREV200100422724  
TI 66 kDa antigen from \*\*\*Borrelia\*\*\*.  
AU Bergstrom, Sven (1); Barbour, Alan George  
CS (1) Umea Sweden  
ASSIGNEE: Symbicom Aktiebolag, Umea, Sweden  
PI US 6204018 March 20, 2001  
SO Official Gazette of the United States Patent and Trademark Office Patents,  
(Mar. 20, 2001) Vol. 1244, No. 3, pp. No Pagination. e-file.  
ISSN: 0098-1133.

DT Patent  
LA English

AB Nucleic acid fragments are disclosed which encode a polypeptide antigen reactive with antisera from rabbits immunised with a 66 kDa protein from \*\*\*Borrelia\*\*\*, \*\*\*garinii\*\*\*, \*\*\*IP90\*\*\*. The presence of nucleic acid fragments encoding such a polypeptide antigen as well as the presence of the polypeptide antigen have been demonstrated in three strains of B. burgdorferi sensu lato, but are substantially absent from at least 95% of randomly selected B. hermsii, B. crociduriae, B. anserina, and B.

hispanica. The encoded polypeptide is surface exposed on the bacterial surface, it is highly conserved, and is thus potentially useful as a vaccine agent and as a diagnostic agent in the diagnosis of infections with *B. burgdorferi* as are the characteristic nucleic acid fragments of the invention. Also disclosed are methods of producing the polypeptide antigen according to the invention as are antibodies directed against the antigen.

TI 66 kDa antigen from \*\*\**Borrelia*\*\*\* .

AB. . . fragments are disclosed which encode a polypeptide antigen reactive with antisera from rabbits immunised with a 66 kDa protein from \*\*\**Borrelia*\*\*\* \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* . The presence of nucleic acid fragments encoding such a polypeptide antigen as well as the presence of the polypeptide antigen. . .

ORGN Super Taxa

Spirochaetaceae: Spirochaetales, Spirochetes, Eubacteria, Bacteria,

Microorganisms

ORGN Organism Name

\*\*\**Borrelia*\*\*\* (Spirochaetaceae)

ORGN Organism Superterms

Bacteria; Eubacteria; Microorganisms

L15 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2

AN 2001:257972 CAPLUS

DN 134:291129

TI Decorin-binding protein genes dbpA and dbpB from \*\*\**Borrelia*\*\*\* species and their use in vaccine compositions

IN Guo, Betty P.; Hook, Magnus

PA Texas A and M University System, USA

SO U.S., 113 pp., Cont.-in-part of U.S. Ser. No. 945,476.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6214355	B1	20010410	US 1998-117257	19980722
	US 5853987	A	19981229	US 1996-589711	19960122
	WO 9727301	A1	19970731	WO 1996-US17081	19961022
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	US 6248517	B1	20010619	US 1997-945476	19971224
	US 6312907	B1	20011106	US 2000-489352	20000121
PRAI US 1995-427023 B2 19950424					
US 1996-589711 A2 19960122					
WO 1996-US5668 A2 19960424					
WO 1996-US17081 W 19961022					
US 1997-945476 A2 19971224					
WO 1996-US5886 A2 19960424					
US 1998-117257 A3 19980722					

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\*Borrelia\*\*\* burgdorferi , the etiol. agent of Lyme disease, and DNA segments encoding dbp from related \*\*\*borrelia\*\*\* . Also disclosed are decorin-binding protein compns. and methods of use. The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathol. \*\*\*Borrelia\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and anti-(decorin binding protein) antibodies will also be of use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\*Borrelia\*\*\* colonization in an animal. These DNA segments and the peptides derived therefrom are contemplated for use in the prepn. of vaccines and, also, for use as carrier proteins in vaccine formulations, and in the formulation of compns. for use in the prevention of Lyme disease. Lyme disease vaccines derived from DbpA and/or DbpB do not suffer the limitations of the prior art, particularly with respect to OspA and other antigens previously investigated as antigens for development of \*\*\*borrelia\*\*\* vaccines.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compositions

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\*Borrelia\*\*\* burgdorferi , the etiol. agent of Lyme disease, and DNA segments encoding dbp from related \*\*\*borrelia\*\*\* . Also disclosed are decorin-binding protein compns. and methods of use. The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathol. \*\*\*Borrelia\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and anti-(decorin binding protein) antibodies will also be of use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\*Borrelia\*\*\* colonization in an animal. These DNA segments and the peptides derived therefrom are contemplated for use in the prepn. of vaccines and, also, for use as carrier proteins in vaccine formulations, and in the formulation of compns. for use in the prevention of Lyme disease. Lyme disease vaccines derived from DbpA and/or DbpB do not suffer the limitations of the prior art, particularly with respect to OspA and other antigens previously investigated as antigens for development of \*\*\*borrelia\*\*\* vaccines.

ST \*\*\*Borrelia\*\*\* decorin binding protein gene sequence; vaccine  
\*\*\*Borrelia\*\*\* decorin binding protein; Lyme disease vaccine decorin binding protein

IT Gene, microbial

RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use);  
BIOL (Biological study); OCCU (Occurrence); USES (Uses)  
(dbpA; decorin-binding protein genes dbpA and dbpB from  
\*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT Gene, microbial

RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use);  
BIOL (Biological study); OCCU (Occurrence); USES (Uses)  
(dbpB; decorin-binding protein genes dbpA and dbpB from  
\*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT Adhesion, biological

\*\*\*Borrelia\*\*\* afzelii

\*\*\*Borrelia\*\*\* andersonii  
\*\*\*Borrelia\*\*\* burgdorferi  
\*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\*  
\*\*\*Borrelia\*\*\* japonica

Lyme disease

Vaccines

(decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT Biglycans

Decorins

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT Proteins, specific or class

RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use);  
BIOL (Biological study); OCCU (Occurrence); USES (Uses)  
(decorin-binding; decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT Proteoglycans, biological studies

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(epiphycans; decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT Proteins, specific or class

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(fibromodulins; decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT Proteoglycans, biological studies

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(lumicans; decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT 184656-08-4 184656-09-5 184656-10-8 184656-11-9 184656-12-0  
184656-13-1 184656-14-2 184656-15-3 200652-16-0 209967-32-8  
218614-69-8 220138-07-8 334072-08-1 334072-11-6 334072-13-8  
334072-14-9 334072-15-0 334072-17-2 334072-18-3 334072-20-7  
334072-21-8 334072-22-9 334072-24-1 334072-26-3 334072-28-5  
334072-30-9 334072-31-0

RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use);  
BIOL (Biological study); OCCU (Occurrence); USES (Uses)  
(amino acid sequence; decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT 184656-16-4 184656-17-5 184656-18-6 184656-19-7 184656-20-0  
184656-21-1 184656-22-2 184656-23-3 189920-72-7 189920-73-8  
208747-09-5 218763-79-2 218763-80-5 218763-81-6 218763-82-7  
218763-83-8 334072-07-0 334072-09-2 334072-10-5 334072-12-7  
334072-16-1 334072-19-4 334072-23-0, DNA ( \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* gene dbpA) 334072-25-2 334072-27-4  
334072-29-6 334072-32-1 334072-33-2

RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use);  
BIOL (Biological study); OCCU (Occurrence); USES (Uses)  
(nucleotide sequence; decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

IT 334072-60-5 334072-61-6 334072-62-7 334072-63-8 334072-64-9  
334072-65-0 334072-66-1, 9: PN: US6214355 SEQID: 10 unclaimed DNA  
334072-67-2

RL: PRP (Properties)

(unclaimed nucleotide sequence; decorin-binding protein genes dbpA and dbpB from \*\*\*Borrelia\*\*\* species and their use in vaccine compns.)

L15 ANSWER 3 OF 21 USPATFULL

AN 2001:196810 USPATFULL

TI DbpA compositions and methods of use

IN Guo, Betty P., Boston, MA, United States  
Hook, Magnus, Houston, TX, United States

PA The Texas A & M University System, College Station, TX, United States  
(U.S. corporation)

PI US 6312907 B1 20011106

AI US 2000-489352 20000121 (9)

RLI Division of Ser. No. US 117257, now patented, Pat. No. US 6214355  
Continuation-in-part of Ser. No. US 945476 Continuation-in-part of Ser.  
No. US 1996-589711, filed on 22 Jan 1996, now patented, Pat. No. US  
5853987 Continuation-in-part of Ser. No. US 1995-427023, filed on 24 Apr  
1995, now abandoned

DT Utility

FS GRANTED

EXNAM Primary Examiner: Zitomer, Stephanie W.

LREP Williams, Morgan and Amerson

CLMN Number of Claims: 35

ECL Exemplary Claim: 1

DRWN 34 Drawing Figure(s); 31 Drawing Page(s)

LN.CNT 5376

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\*Borrelia\*\*\* burgdorferi, the etiological agent of Lyme disease, and DNA segments encoding dbp from related \*\*\*borrelia\*\*\*. Also disclosed are decorin binding protein compositions and methods of use. The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathological \*\*\*Borrelia\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and anti-(decorin binding protein) antibodies will also be of use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\*Borrelia\*\*\* colonization in an animal. These DNA segments and the peptides derived therefrom are contemplated for use in the preparation of vaccines and, also, for use as carrier proteins in vaccine formulations, and in the formulation of compositions for use in the prevention of Lyme disease.

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\*Borrelia\*\*\* burgdorferi, the etiological agent of Lyme disease, and DNA segments encoding dbp from related \*\*\*borrelia\*\*\*. Also disclosed are decorin binding protein compositions and methods of use.

The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathological \*\*\*Borrelia\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and . . . of use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\*Borrelia\*\*\* colonization in an animal. These DNA segments and the peptides derived therefrom are contemplated for use in the preparation of . . .

SUMM . . . proteins derived from bacterial species. More particularly, the

invention provides gene compositions encoding the decorin (Dcn) binding proteins (DBPs) from \*\*\*Borrelia\*\*\* burgdorferi and the corresponding peptide epitopes and protein sequences comprising native and synthetically-modified Dcn binding site domains. Various methods for. . .

SUMM Lyme disease (Steere, 1989), or Lyme \*\*\*borreliosis\*\*\*, is transmitted by ticks, particularly of the genus Ixodes, and caused by spirochetes of the genus \*\*\*Borrelia\*\*\*. Lyme disease agents, that is \*\*\*borrelia\*\*\* isolated from humans or animals with clinical Lyme disease, are currently classified into at least four phylogenetic groups: B. burgdorferi sensu stricto, B. \*\*\*garinii\*\*\*, B. andersonii, and B. afzelii. Strains potentially representing other phylogenetic groups of Lyme disease agents as well, such as group. . .

SUMM . . . vitro-grown or tick-borne B. burgdorferi. Based largely on the protective efficacy of experimental OspA vaccines in rodent models of Lyme \*\*\*borreliosis\*\*\*, three monovalent OspA-based vaccines are currently in clinical trials. However, recent findings suggest that broad, sustained protection of humans may. . .

SUMM c) OspA is serologically diverse, particularly among European and Asian B. \*\*\*garinii\*\*\* and B. afzelii isolates. Reactivity with panels of OspA monoclonal antibodies (mAbs), and DNA sequence analysis has shown that as. . .

SUMM . . . and Bockenstedt, 1993). OspA is expressed by B. burgdorferi within ticks (Barbour et al., 1983), but detection of OspA on \*\*\*borrelia\*\*\* in tissue early after infection is difficult. Passive immunization of mice with OspA antibody (Schaible et al., 1990), or immunization. . .

SUMM . . . vivo only at later stages when the infection becomes disseminated. This would be explained by down-regulation of OspA expression by \*\*\*borrelia\*\*\* shortly after initiation of feeding by the tick.

SUMM . . . et al. (1996) demonstrated that when OspA-specific antibodies were administered to mice before or at the time of attachment of \*\*\*borrelia\*\*\*-infected ticks these mice were protected from spirochetal infection. However, when OspA-specific antibody was administered 48-hr after tick attachment no protection. . .

SUMM Modulation of \*\*\*borrelia\*\*\* antigen expression within feeding ticks has recently been reported for OspC; initially low in resting ticks, OspC levels increase on. . .

SUMM . . . to pre-exist at high levels in human or animal hosts prior to the tick bite to be effective against OspA-expressing \*\*\*borrelia\*\*\* in the tick, and may receive little or no boosting upon delivery of the spirochetes into the skin within the. . .

SUMM . . . the gut of the infecting tick, before inoculation of the pathogen." Consistent with this hypothesis it has been shown that anti- \*\*\*borrelia\*\*\* serum can protect mice from infection by tick bite if administered within two days after initiation of feeding by \*\*\*borrelia\*\*\*-infected ticks, but not when passively administered at later times (Shih et al., 1995). The antibody levels in response to recombinant. . .

SUMM . . . the host cell ECM component, Dcn. Also disclosed are methods for active and passive immunization against B. burgdorferi and related \*\*\*borrelia\*\*\* including B. afzelii, B. andersonii, B. japonica, and B. \*\*\*garinii\*\*\* using novel native and site-specifically-altered DBP compositions and DBP-derived epitopic peptides from B. burgdorferi,

B. andersonii, B. afzelii, B. japonica, and B. \*\*\*garinii\*\*\* .  
Particular aspects of the invention relate to novel nucleic acid  
segments encoding these peptides and epitopes, and methods for the. .

SUMM . . . include the dbpA and dbpB genes, in particular those from B.  
burgdorferi, B. japonica, B. andersonii, B. afzelii, and B.  
\*\*\*garinii\*\*\* .

SUMM . . . ID NO:22, SEQ ID NO:24, or SEQ ID NO:26 encoding the DbpA  
protein of strains 297, B31, Sh.2.82, HB-19, PGau, \*\*\*IP90\*\*\* , LP4,  
LP7, and JD1, respectively, or to the nucleic acid sequence of SEQ ID  
NO:29, SEQ ID NO:31, SEQ ID . . . ID NO:51, encoding the DbpA protein  
of strains 297/LP4, SH2, N40, JD1, HB19, B31/BR4/3028, G3940, LP4, ZS7,  
PGau, B023, and \*\*\*IP90\*\*\* , respectively.

SUMM . . . PKo (DbpB protein: SEQ ID NO:62), HB19, G3940, LP5, ZS7, NCH-1,  
FRED, and 20047 (DbpB protein: SEQ ID NO:64) and \*\*\*IP90\*\*\* (DbpB  
protein: SEQ ID NO:66), respectively.

SUMM SEQ ID NO:7 lists the nucleotide sequence of a 2.5-kb insert of  
\*\*\*borrelia\*\*\* genomic DNA cloned in pBlueScript.TM. which comprises  
the dbpA and dbpB genes of B. burgdorferi 297. This recombinant clone,  
designated. .

SUMM . . . respectively. Strain variants are those nucleic acid  
compositions and polypeptide compositions expressed by various strains  
of B. burgdorferi and related \*\*\*borrelia\*\*\* including B. afzelii,  
B. andersonii, B. japonica, and B. \*\*\*garinii\*\*\* which specifically  
encode DBPs.

SUMM . . . DbpA and DbpB proteins of B. burgdorferi strain 297. Such DbpA  
amino acid sequences include those DbpA sequences of related  
\*\*\*borrelia\*\*\* strains B31, Sh.2.82, HB-19, LP4, LP7, and JD1 of B.  
burgdorferi (SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, . . . ID NO:22,  
SEQ ID NO:24, and SEQ ID NO:26, respectively); strain pGau (SEQ ID  
NO:18) of B. afzelii; or strain \*\*\*IP90\*\*\* (SEQ ID NO:20) of B.  
\*\*\*garinii\*\*\* . DbpA amino acid sequences are also disclosed in SEQ ID  
NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, . .

SUMM . . . alternatively by demonstrating the ability of the  
strain-variant DBPs to lessen or prevent adherence of B. burgdorferi and  
related \*\*\*borrelia\*\*\* including B. afzelii, B. andersonii, B.  
japonica, and B. \*\*\*garinii\*\*\* to Dcn.

SUMM . . . ID NO:49, and SEQ ID NO:51, and all strain variants or active  
fragments thereof encoding all or portions of a \*\*\*borrelia\*\*\* DbpA  
protein.

SUMM . . . NO:56), and FIG. 11 (SEQ ID NO:54) or strain variants or active  
fragments thereof encoding all or portions of a : \*\*\*borrelia\*\*\*  
DbpB protein.

SUMM . . . is also understood to comprise one or more polypeptides that  
are immunologically reactive with antibodies generated against B.  
burgdorferi, B. \*\*\*garinii\*\*\* , B. afzelii, B. andersonii, B.  
japonica, or related \*\*\*Borrelia\*\*\* spp. and in particular  
antibodies generated against a DbpA or DbpB protein, particularly those  
encoded by the dbpA nucleic acid. . .

SUMM . . . a treated animal, this immune response being effective to  
lessen or prevent symptomatic disorders associated with Lyme disease or  
related \*\*\*borrelioses\*\*\* , or which polypeptides are capable of  
eliciting antibodies that are immunologically reactive with a DbpA  
encoded by a nucleic acid. . .

SUMM . . . concern isolated DNA segments and recombinant vectors encoding

one or more DBPs, in particular, the DbpA and DbpB proteins from \*\*\*Borrelia\*\*\* such as B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, and B. japonica, and the creation and use of recombinant host cells through the application of DNA technology, that express one or more dbp gene products, and in particular, the dbpA and dbpB genes from \*\*\*Borrelia\*\*\* such as B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, and B. japonica,. As such, the invention concerns DNA segments comprising an isolated gene that encodes a DbpA protein or. . .

SUMM . . . or DbpB protein, and more preferably, comprises a dbpA or dbpB gene, in particular, a dbpA or dbpB gene from \*\*\*Borrelia\*\*\* such as B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, or B. japonica. In this respect, the term "gene" is used for simplicity to refer to a functional protein, polypeptide. . .

SUMM . . . and DBP peptides, in particular those DBPs isolated from prokaryotic sources such as bacteria. DNA segments isolated from species of \*\*\*Borrelia\*\*\* and related bacteria which are shown to bind Dcn are particularly preferred for use in the methods disclosed herein. Such. . .

SUMM . . . to be useful in the production of anti-DbpA or anti-DbpB antibodies for use in passive immunization methods for prevention of \*\*\*borrelial\*\*\* adhesion to Dcn, and treatment of infections due to \*\*\*Borrelia\*\*\* invasion, and particularly invasion by B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, or B. japonica. Such anti-DbpA or anti-DbpB antibodies are also contemplated for use in passive immunization methods for prevention of. . .

SUMM . . . may be employed in connection with "overexpressing" DBPs, that is, increasing the level of expression over that found naturally in \*\*\*Borrelia\*\*\*, in particular, B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, B. japonica, or related spirochete.

SUMM . . . proteins of the present invention are contemplated to have affinity for Dcn and may be purified from other constituents of \*\*\*Borrelia\*\*\*, in particular, B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, or B. japonica, or recombinant host cells by chromatography on matrices containing Dcn, so-called "affinity chromatography." DBPs may also be. . .

SUMM . . . one or more dbp genes or dbp-derived DNA segments, and recombinant vectors and transformed host cells comprising one or more \*\*\*Borrelia\*\*\* dbp-derived nucleic acid segments, in particular one or more dbpA or dbpB nucleic acid segments from B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, or B. japonica. As is well known to those of skill in the art, many such vectors and host cells. . . long as the coding segment employed encodes a protein or peptide of interest (e.g., a DbpA or DbpB protein from \*\*\*Borrelia\*\*\*, and particularly a DbpA or DbpB protein from B. burgdorferi, B. afzelii, B. andersonii, B. japonica, or B. \*\*\*garinii\*\*\*, and does not include any coding or regulatory sequences that would have an adverse effect on cells.

Therefore, it will. . .

SUMM . . . direct the expression and production of the protein or peptide epitope of interest (e.g., a DbpA or DbpB protein from \*\*\*Borrelia\*\*\* and in particular, from B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, or B. japonica) when incorporated into a host cell. In a recombinant expression vector, the coding portion of the DNA. . .

SUMM . . . and in particular DbpA or DbpB are useful as diagnostic probes to detect the presence of B. burgdorferi, and related \*\*\*borrelias\*\*\*

including *B. afzelii*, *B. andersonii*, *B. japonica*, and *B. \*\*\*garinii\*\*\** in a test sample, using conventional techniques. In one such method of diagnosing \*\*\**Borrelia*\*\*\* infection, *DbpA* and/or *DbpB* nucleic acid segments may be used in Southern hybridization analyses or Northern hybridization analyses to detect. . .

SUMM . . . antibodies for diagnostic and therapeutic methods relating to the detection and treatment of infections caused by *B. burgdorferi* and related \*\*\**borrelia*\*\*\* including *B. afzelii*, *B. andersonii*, *B. \*\*\*garinii\*\*\**, and *B. japonica*.

SUMM . . . are useful to generate pure recombinant DBP for administration to a host. Such administration is useful to prevent adherence of \*\*\**Borrelia*\*\*\* spp., and in particular, *B. burgdorferi*, *B. afzelii*, *B. andersonii*, *B. \*\*\*garinii\*\*\**, and *B. japonica*, to the host's tissues or as a vaccine to induce therapeutic antibodies.

SUMM . . . raised against and reactive with one or more DBPs is inhibitory to in vitro and in vivo growth of various \*\*\**Borrelia*\*\*\* strains. Thus, it is contemplated that administration of antibodies reactive with one or more DBPs to at-risk subjects will be. . .

SUMM . . . serum concentration of DBP-reactive antibodies that is at least twice that required for inhibition of in vitro growth of endemic \*\*\**borrelia*\*\*\* strains. It is contemplated that the duration of dosing maintaining anti-*DbpA* and or anti-*DbpB* levels at these inhibitory antibody concentrations would be for at least four to eight weeks following presumptive exposure to a \*\*\**Borrelia*\*\*\*, and in particular, *B. burgdorferi*, or throughout the duration of symptoms of Lyme disease and for at least four to. . .

SUMM . . . length will often be preferred. The antigenic proteins or peptides may also be combined with other agents, such as other \*\*\**borrelial*\*\*\* peptide or nucleic acid compositions, if desired.

SUMM . . . methods for the stimulation of an immune response include vaccination regimens designed to prevent or lessen significant infections caused by \*\*\**borrelia*\*\*\* or other bacteria expressing a DBP, and treatment regimens that may lessen the severity or duration of any infection, it. . . be used particularly for the treatment of infections caused by pathogens such as *B. burgdorferi*, *B. afzelii*, *B. andersonii*, *B. \*\*\*garinii\*\*\**, *B. japonica*, related \*\*\**borrelial*\*\*\* species, and other bacteria which express one or more DBPs and in particular *DbpA* and/or *DbpB* and adhere to Dcn.

SUMM Immunoformulations of this invention, whether intended for vaccination, treatment, or for the generation of antibodies useful in the detection of \*\*\**borrelia*\*\*\* and in particular *B. burgdorferi*, the prevention of bacterial adhesion, or in the case of bacterial colonization, promotion of bacterial. . .

SUMM . . . in the immunodetection of compounds, present within clinical samples, that are indicative of Lyme disease or related infections caused by \*\*\**borrelia*\*\*\*, and in particular *B. burgdorferi*. The kits may also be used in antigen or antibody purification, as, appropriate.

SUMM . . . even perhaps urine samples may be employed. This allows for the diagnosis of Lyme disease and related infections caused by \*\*\**borrelia*\*\*\*, and in particular, *B. burgdorferi*. Furthermore, it is contemplated that such embodiments may have application to non-clinical samples, such as. . .

SUMM . . . therapeutically effective dose of *DbpA* and/or *DbpB* to a subject induces in the subject antibodies which bind and neutralize a

\*\*\*Borrelia\*\*\* bacterium (and particularly B. burgdorferi, B. \*\*\*garinii\*\*\*, B. afzelii, B. andersonii, B. japonica and related \*\*\*Borrelia\*\*\* spp.), present in the subject, thereby preventing the deleterious effects of this microorganism. Alternatively, anti- \*\*\*Borrelia\*\*\* antibodies, and in particular, anti-B. burgdorferi, B. \*\*\*garinii\*\*\*, B. afzelii, B. andersonii, B. japonica and related \*\*\*Borrelia\*\*\* spp. antibodies generated in a first host animal provide antibodies which can be administered to a second subject for passive immunization or treatment against B. burgdorferi, B. \*\*\*garinii\*\*\*, B. afzelii, B. andersonii, or B. japonica infection. Such anti- \*\*\*Borrelia\*\*\* antibodies are also useful as a diagnostic screen for the presence of \*\*\*Borrelia\*\*\*, and in particular B. burgdorferi, B. \*\*\*garinii\*\*\*, B. afzelii, B. andersonii, B. japonica or related \*\*\*Borrelia\*\*\* spp. In a test sample, using conventional immunoassay techniques.

SUMM . . . SEQ ID NO:61, SEQ ID NO:63 or SEQ ID NO:65) encode novel DBPs of B. burgdorferi, B. afzelii, and B. \*\*\*garinii\*\*\*. Strain variants are prepared and screened by amplification of nucleic acid sequences of other strains of B. burgdorferi or similar. . .

SUMM . . . vaccine compositions useful in the prevention of Lyme disease and antibody compositions useful in the prevention of Dcn binding to \*\*\*Borrelia\*\*\*.

SUMM . . . bacterial cells. These aspects provide methods and compositions for producing bacterial colonization of an animal host with attenuated, or avirulent \*\*\*Borrelia\*\*\* expressing cell surface DBP epitopes.

SUMM . . . with an antibody composition disclosed herein, and detecting the formation of immune complexes. In preferred embodiments, the bacterium is a \*\*\*borrelia\*\*\*, and most preferably a B. burgdorferi, B. afzelii, B. andersonii, or B. \*\*\*garinii\*\*\* strain.

SUMM . . . include pharmaceutically-acceptable formulations of either the antibodies or peptide antigens disclosed herein. Such kits are useful in the detection of \*\*\*borrelia\*\*\* in clinical samples, and also useful for inhibiting or promoting the binding of \*\*\*borrelia\*\*\* to the ECM component, Dcn. In preferred embodiments, the bacteria detected using such kits include \*\*\*borrelia\*\*\*, and in particular, B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, B. japonica, and related species.

SUMM Other aspects of the invention include methods of inhibiting bacterial colonization, and particularly colonization by \*\*\*borrelia\*\*\*, in an animal by administering to the animal an antibody of the present invention which prevents or significantly reduces the. . . the antibody composition may be prophylactically prior to and/or following diagnosis of Lyme disease or other multisystemic disorders caused by \*\*\*Borrellooses\*\*\* which may, involve the skin, joints, heart, and central nervous system. The administration may also be made in passive immunization. . .

SUMM . . . other Gram-negative hosts including various Pseudomonas species may be used in the recombinant expression of the genetic constructs disclosed herein. \*\*\*Borrelia\*\*\* themselves may be used to express these constructs, and in particular, B. burgdorferi, B. afzelii, B. andersonii, B. japonica and B. \*\*\*garinii\*\*\*.

DRWD FIG. 6. Nucleotide sequence of B. burgdorferi dbpB gene from strains HB19, G3940, LP5, ZS7, NCH01, FRED, and B. \*\*\*garinii\*\*\* dbpB gene from strain 20047. The sequence is identical for all seven strains (SEQ ID NO:63). The translated amino acid sequence of B. burgdorferi DbpB

protein from strains HB19, G3940, LP5, ZS7, NCH01, FRED, and B.

\*\*\*garinii\*\*\* DbpB protein from strain 20047 is also identical for all seven strains (SEQ ID NO:64).

DRWD FIG. 8. Partial dbpB gene sequence from B. \*\*\*garinii\*\*\* strain \*\*\*IP90\*\*\* (SEQ ID NO:65) and corresponding amino acid sequence of DbpB protein (SEQ ID NO:66).

DRWD FIG. 12. Nucleotide and deduced amino acid sequence of B.

\*\*\*garinii\*\*\* strain \*\*\*IP90\*\*\* dbpA gene (SEQ ID NO:51). The translated amino acid sequence of DbpA is given in SEQ ID NO:52.

DRWD FIG. 22. Comparison of amino acid sequence identities for the DbpAs from related \*\*\*borrelia\*\*\*. The predicted DbpA amino acid sequences disclosed herein were compared in a pairwise fashion as to % identity using the . . .

DETD . . . is anticipated to be especially effective in treatment regimens for Lyme disease, and as a cost-effective prophylaxis for prevention of \*\*\*borrelial\*\*\* infections.

DETD . . . of OspA as antibodies reactive with DbpA-derived from B. burgdorferi sensu stricto are also growth-inhibitory to many strains of B. \*\*\*garinii\*\*\* and B. afzelii;

DETD (3) Antiserum against DbpA.sub.297 provides either complete or partial protection against several additional heterologous B. burgdorferi, B. afzelii, and B. \*\*\*garinii\*\*\* strains;

DETD . . . and isolate molecular clones of alleles of this gene present in different phylogenetic groups of Lyme disease spirochetes including B. \*\*\*garinii\*\*\*, B. japonica, B. afzelii, B. andersonii, and related \*\*\*Borrelia\*\*\* spp. by utilization of PCR.TM. techniques. These new dbp alleles have been shown to have a high level of sequence. . .

DETD . . . limitations of the prior art, particularly with respect to OspA and other antigens previously investigated as antigens for development of \*\*\*borrelia\*\*\* vaccines. Indeed, vaccine compositions comprising one or more DBPs, and in particular, DbpA and/or DbpB, are likely to be superior. . .

DETD . . . as antibodies reactive with DbpA and DbpB derived from B. burgdorferi sensu stricto are also growth-inhibitory to strains of B. \*\*\*garinii\*\*\* and B. afzelii.

DETD 4.2.5 Anti-DbpA or Anti-DbpB Antibodies Eliminate \*\*\*Borrelia\*\*\* From Infected Animals

DETD 4.2.6 dbp Nucleic Acid Segments Are Useful in Identifying \*\*\*Borrelial\*\*\* Isolates

DETD . . . molecular clones of alleles of this gene present in different phylogenetic groups of Lyme disease spirochetes including B. burgdorferi, B. \*\*\*garinii\*\*\*, B. afzelii, B. andersonii, and B. japonica by utilization of such techniques as PCR.TM..

DETD . . . binding Dcn, Fmn, Bgn, Epn, or Lmn. Exemplary and preferred dbp genes include the dbpA and dbpB genes isolated from \*\*\*Borrelia\*\*\*, and in particular, from B. burgdorferi, B. afzelii, B. andersonii, B. \*\*\*garinii\*\*\*, or B. japonica.

DETD . . . and/or dbpB gene products encoded by such nucleic acid segments, or in the production of diagnostic and treatment protocols for \*\*\*borrelia\*\*\* infection, and in particular, infection with B. burgdorferi, B. afzelii, B. andersonii, B. japonica, or B. \*\*\*garinii\*\*\*, and those infections leading to Lyme disease. Any and all such combinations are intended to fall within the scope of . . .

DETD . . . from which the DBP composition(s) may be applied to a tissue site, skin lesion, wound area, or other site of \*\*\*borrelial\*\*\*

infection. However, the single container means may contain a dry, or iyophilized, mixture of one or more DBP composition(s), which. . . DETD . . . the DBP composition to the body, bloodstream, or to a tissue site, skin lesion, wound area, or other site of \*\*\*borrelial\*\*\* infection. Such deliver device may or may not itself contain a sterile solution, diluent, gelatinous matrix, carrier or other pharmaceutically-acceptable. . .

DETD . . . analyze the distribution of bacteria expressing DBPs during cellular infection, for example, to determine the cellular or tissue-specific distribution of \*\*\*borrelia\*\*\* under different physiological conditions. A particularly useful application of such antibodies is in purifying native or recombinant DBPs, for example,. . .

DETD 4.14 DBP Compositions for Treating \*\*\*Borrelia\*\*\* Infections  
DETD . . . quantities. The selected antigens, and variants thereof, are proposed to have significant utility in diagnosing and treating infections cause by \*\*\*borrelia\*\*\* and in particular, B. burgdorferi, B. \*\*\*garinii\*\*\*, B. andersonii, B. japonica and B. afzelii. For example, it is proposed that rDBPs, peptide variants thereof, and/or antibodies against such rDBPs may also be used in immunoassays to detect \*\*\*borrelia\*\*\* or as vaccines or immunotherapeutics to treat \*\*\*borrelia\*\*\* infections, and to prevent bacterial adhesion to ECM components such as Dcn in the same manner as native DBP compositions. . .

DETD . . . The peptides provided by this invention are ideal targets for use as vaccines or immunoreagents for the treatment of various \*\*\*borrelia\*\*\* -related diseases, and in particular, those caused by species which contain DBP and DBP-encoding genes, and hence those which express either. . .

DETD The \*\*\*Borrelia\*\*\* binding site on the Dcn molecule has not been identified. Presumably, Dcn binds both collagen and \*\*\*borrelia\*\*\* at once, with the two interactions involving different sites on the proteoglycan. The requirement of intact Dcn adhesin on the. . .

DETD . . . adhesive function of DBPs, and their role as targets for growth-inhibitory, antibodies imply that the DBPs are localized to the \*\*\*borrelia\*\*\* outer membrane. To provide additional biochemical support for this B. burgdorferi B3 total membranes were separated into inner and outer. . . centrifugation technique (Bledsoe et al., 1994). By detergent phase portioning DbpA appears to be amphiphilic as are OspA and other \*\*\*borrelia\*\*\* membrane lipoproteins (Brandt et al. 1990). To confirm the presence of lipid on these proteins B. burgdorferi B31 was metabolically. . .

DETD . . . of DBPs for 1 hour before allowing a suspension of B. burgdorferi to attach. Both DbpA:549 and DbpA:C25A can inhibit \*\*\*Borrelia\*\*\* attachment to Dcn-coated microtiter wells. Attachment of B. burgdorferi 297 is completely blocked when the wells are preincubated with 600. . . when preincubated with 400 ng (FIG. 26B). For N40, DbpB appeared to inhibit attachment weakly. This data suggested that different \*\*\*Borrelia\*\*\* strains may vary in their expression of DBPs. Alternatively, the two proteins could bind to different binding sites on Dcn.

DETD A Western blot was used to address whether different \*\*\*Borrelia\*\*\* strains express different relative amounts of the two DBPs. Rabbit anti-sera were generated against DbpA:549 and DbpB:500. Surprisingly, these anti-sera. . .

DETD . . . difference may be an artifact resulting from using purified proteins in an in vitro assay since the DBPs present in \*\*\*Borrelia\*\*\* membranes may not be fully accessible.

DETD Identification of DBPs in \*\*\*Borrelial\*\*\* Isolates

DETD One aspect of the present invention, is the identification of \*\*\*borrelia\*\*\* using the DBP compositions disclosed herein as diagnostic indicators of \*\*\*borrelial\*\*\* infection. As shown in Table 2 an assay of DBPs in \*\*\*borrelia\*\*\* using Western hybridization analyses, it was possible to identify the presence of DBPs in at least 13 strains of *B. burgdorferi*, 5 strains of *B.*

\*\*\*garinii\*\*\*, and at least three strains of *B. afzelii*. These methods represent important diagnostic tools for the identification of bacteria in. . .

DETD TABLE 2

Assay of DBPs in \*\*\*Borrelia\*\*\* By Western Blot

Strain	Origin	DBP	Source
--------	--------	-----	--------

*B. burgdorferi*

sensu stricto

CA3 tick + R. Lane

CA7 tick + R. Lane

CA8 tick + R. Lane

CA20. . . *I. ricinus*, Germany ++

H11 Blood, Italy +

CA-3-87 *I. pacificus*, USA (CA) .+.

FRED (human), USA (MO) -

HBNC Blood, USA (CA) .+.

*B. \*\*\*garinii\*\*\**

PBr CSF, Germany ++

PBi CSF, Germany ++

B4 91 Skin, Norway ++

G2.22 CSF, Germany ++

\*\*\*Ip90\*\*\* *I. persulcatus*, Russia +

IP89 *I. persulcatus*, Russia ++

2226 *I. persulcatus*, China +

Fuji P1 *I. persulcatus*, Japan ++

20047 *I. ricinus*, France. . .

DETD . . . the DbpA DNA sequence of strain 297 were used as primers for

PCR.TM. amplifications of dbp gene fragments from various

\*\*\*borrelia\*\*\* strains. Using a western blot-like assay with tagged

Dcn for assessment of Dcn binding activity, almost all strains were

found. . .

DETD The sequence divergence of DbpA from some *B. afzelii* and *B.*

\*\*\*garinii\*\*\* strains PGau with respect to the *B. burgdorferi* strains

is consistent with the resistance of these strains to in vitro growth

inhibition by anti-DbpA.sub.297 serum. Availability of the dbpA

sequences from *B. afzelii* and *B. \*\*\*garinii\*\*\** provides a the basis

for obtaining clones of additional *B. afzelii* and *B. \*\*\*garinii\*\*\**

dbpA gene sequences, elucidation of the common epitope motifs which may

differ from *B. burgdorferi* and facilitate design of broad. . .

DETD DBP Compositions Block Adherence of \*\*\*Borrelia\*\*\* to Dcn

DETD Inhibitory Activity of anti-rDbpA Serum Towards \*\*\*Borrelial\*\*\*

Growth

DETD Two other \*\*\*borrelial\*\*\* proteins, OspA and OspB, believed to be

surface-exposed have been shown to be targets for bacterial killing by

specific antibodies. . .

DETD Table 6 shows the growth inhibitory activity of anti-rDbpA serum for diverse \*\*\*borrelia\*\*\* strains. The sensitivity of *B. burgdorferi* to growth in the presence of various antibodies in the absence of complement was. . . assay performed in microtiter plates. Rabbit antisera were serially diluted in 96-well plates in 0.1 ml BSKII medium, 10  $\mu$ l in the mid-log phase of growth in 0.1 ml BSKII medium were added per well, the mixture was incubated for. . . expressing DbpA (HB-19, CA-3-87, and FRED express little or no DbpA in vitro), as well as several of the *B. \*\*\*garinii\*\*\** and *B. afzelii* strains. Three *B. afzelii* strains and one *B. \*\*\*garinii\*\*\** strain were slightly inhibited at a 1:50 serum dilution. Strain 25015 was also inhibited by 1:10 anti-DBP serum. *B. andersonii*. . . from strain 297 inhibit the growth of more strains than anti-OspA serum, anti-DbpA antibodies inhibit more *B. afzelii* and *B. \*\*\*garinii\*\*\** strains than OspA. As some strains failed to express DbpA in vitro (as judged by Dcn- and immuno-blotting, the determination that 20 of 36 strains are sensitive to inhibition by anti-DbpA may be an underestimate.

\*\*\*Borrelia\*\*\* strains were obtained from Drs. Steve Norris, John Leong, Alan Barbour, Robert Lane, Robin Isaacs, David Dorward, and Steve Barthold.

DETD	1,600	++			
FRED	(human), USA (MO)	1,600	+	3,200	++
HBNC	Blood, USA (CA)	3,200	.+-.	3,200	++
	3 pos./7		2 pos./17		

#### *B. \*\*\*garinii\*\*\**

PBr	CSF, Germany	12,800	+	<50	++
PBi	CSF, Germany	800	-	<50	++
B4 91	Skin, Norway	<100	-	<50	++
G2.22	CSF, Germany	<50	-	<50	++

\*\*\*Ip90\*\*\* I. persulcatus, Russia <50 .+->50 ++  
 IP89 I. persulcatus, Russia <50 - <50 +  
 2226 I. persulcatus, China 200 .+->50. .

DETD . . . of the donors can be purified and systemically administered to a target population. Those individuals at high risk for developing \*\*\*borrelia\*\*\* infections include, but are limited to, patients in intensive care units, immunocompromised patients, surgery patients, children, and persons in areas. . . infestations such as the northeastern, midwestern, and western pacific United States. Two particular references which describe those at risk from

\*\*\*borrelioses\*\*\* include Steere, 1994 and a report by the Centers for Disease Control, 1994.

DETD . . . that accessibility of DbpA to antibodies is not an artifact of in vitro manipulation is to demonstrate passive protection from \*\*\*borrelia\*\*\* challenge with these antibodies. Even though common strains of inbred mice (such as C3H/HeJ, C3H/HeN, and Balb/cByJ) may differ in the severity of disease elicited by \*\*\*borrelia\*\*\*, their sensitivities to infectious \*\*\*borrelia\*\*\* strains is more uniform.

DETD . . . no serum. At two weeks post-challenge tissue samples (bladder, heart, synovial fluid) were placed in BSKII medium and evidence of \*\*\*borrelia\*\*\* outgrowth from these tissues were assessed microscopically after 2 and 3 weeks of in vitro culture. Protection was judged to. . .

DETD . . . to infection. This suggests that an infection-induced memory response to OspA will be of little or no benefit. However, other \*\*\*borrelia\*\*\* surface proteins required for growth and persistence in

vivo may not suffer this limitation as vaccine immunogens. Many bacterial pathogens including \*\*\*borrelia\*\*\* initiate infection following adhesion to specific macromolecules of the host target tissue. These adhesins are exposed at the bacterial surface. . .

DETD . . . favorable pharmacokinetics. The studies measured only infection rather than disease, however, antibody levels which are not sufficient to eliminate all \*\*\*borrelia\*\*\* may in fact be sufficient to prevent disease pathologies.

DETD Isolation of Nucleic Acid Sequences Encoding DBPs from *B. burgdorferi*, *B. afzelii*, and *B. \*\*\*garinii\*\*\**

DETD Oligonucleotides were used as primers for PCR.TM. amplifications of dbpA gene fragments from \*\*\*borrelia\*\*\* strains representing the three major phylogenetic groups of Lyme disease spirochetes. Primers derived from the dbpA gene of strain 297. . .

DETD Identification of candidate dbpA alleles from *B. burgdorferi*, *B. afzelii*, and *B. \*\*\*garinii\*\*\** was accomplished using oligonucleotides as primers for PCR.TM. amplifications of dbpA gene fragments from \*\*\*borrelia\*\*\* strains representing the three major phylogenetic groups of Lyme disease spirochetes. Portions of the PCR.TM. amplification reactions were electrophoresed on. . .

DETD Table 9 shows a summary of the heterologous \*\*\*borrelia\*\*\* strain passive protection results discussed in Example 5.10. Data were compiled in tabular form and expressed as % of mice. . .

#### DETD TABLE 7

Effect of Post-Challenge Passive Administration of Antisera on \*\*\*Borrelia\*\*\* Infection in C3H/HeJ Mice

Number of Mice Infected

at Each Day of Serum Administration

Antiserum	0	2	4	7	10
-----------	---	---	---	---	----

DbpA	0/3.	. . .
------	------	-------

DETD Identification of candidate dbpB alleles from *B. burgdorferi*, *B. afzelii* and *B. \*\*\*garinii\*\*\** was accomplished using oligonucleotides derived from the strain 297 dbpB gene sequence as PCR.TM. primers in a manner similar to. . . *burgdorferi* (2P4, Sh2, FRED, G39/40, WB 19, LP5, NCH-1, Zs7, LP7, N40, CA-2-87, JD1, IPS, *B. afzelii* (Pko), and *B. \*\*\*garinii\*\*\** (20047) strains. At the amino acid level the DbpB proteins expressed by these 16 dbpB genes share >98% amino acid. . .

#### DETD TABLE 8

Amplification of a DBP Allele from Various \*\*\*Borrelia\*\*\* spp.

DBP	DBP	DBP	DBP	DBP
Full Length	Truncate	Pair 1	Pair 2	Pair

3

Species	Strain	Expected	564 bp	448. . .	+
	Sh.2.82	+	+	++	+
<i>B. afzelii</i>	ACA-1	+	-	- +	-
	PGau	+	+	---	
<i>B. ***garinii***</i>	***IP90***		+	+	---
	B491	+	-	---	
	pBi	-	-	---	

#### DETD TABLE 9

Anti-DBP Serum	Anti-OspA Serum	Challenge Culture Positive Tissues	Culture Positive Tissues
***Borrelia***	% of Mice	% of Mice	
Strain	Bladder Ear	Protected Bladder Ear	Protected
<i>B. burgdorferi</i> sensu stricto			

B31 0/5 0/5 100% 0/5 0/5. . .

DETD SEQ ID NO:20, dbpA gene from B. \*\*\*garinii\*\*\* strain \*\*\*IP90\*\*\* .  
DETD SEQ ID NO:21, DbpA protein from B. \*\*\*garinii\*\*\* strain \*\*\*IP90\*\*\*

DETD SEQ ID NO:43, dbpA gene from B. burgdorferi \*\*\*IP90\*\*\* .  
DETD SEQ ID NO:51, dbpA gene from B. \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* .  
DETD SEQ ID NO:52, DbpA protein from B. \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* .  
DETD SEQ ID NO:63, dbpB gene from B. burgdorferi HB19, G3940, LP5, ZS7,  
NCH-1, FRED, and B. \*\*\*garinii\*\*\* 20047.  
DETD SEQ ID NO:64, DbpB protein from B. burgdorferi HB19, G3940, LP5, ZS7,  
NCH-1, FRED, and B. \*\*\*garinii\*\*\* 20047.  
DETD SEQ ID NO:65, Partial dbpB gene from B. \*\*\*garinii\*\*\* \*\*\*IP90\*\*\*

DETD SEQ ID NO:66, Partial DbpB protein from B. \*\*\*garinii\*\*\*  
\*\*\*IP90\*\*\* .

DETD Barthold et al., "Animal Model: Chronic Lyme \*\*\*borreliosis\*\*\* in  
the Laboratory Mouse," Am. J. Pathol., 143:959-971, 1993.

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(ed.), Cold Spring Harbor Press, Plainview, . . .

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L15 ANSWER 4 OF 21 USPATFULL

AN 2001:173362 USPATFULL

TI Methods and compositions including a 13kD B. burgdorferi protein

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1992-924798, filed on 6 Aug 1992, now abandoned Continuation of Ser. No.  
US 1989-422881, filed on 18 Oct 1989, now abandoned

PRAI DK 1988-5902 19881024

DT Utility

FS GRANTED

EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Swartz, Rodney

P.

LREP Frommer Lawrence & Haug LLP, Kowalski, Thomas J.

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 5 Drawing Page(s)

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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB All \*\*\**Borrelia*\*\*\* *burgdorferi* sensu lato isolates characterized to date have one or a combination of several major outer surface proteins (Osp). Mutants of *B. burgdorferi* lacking Osp proteins were selected with polyclonal or monoclonal antibodies at a frequency of 10.sup.-6 to 10.sup.-5. One mutant that lacked OspA, B, C and D was further characterized in the present study. It was distinguished from the OspA.sup.+ B.sup.+ cells by its (i) auto-aggregation and slower growth rate, (ii) decreased plating efficiency on solid medium, (iii) serum- and complement-sensitivity, and (iv) diminished capacity to adhere to human umbilical vein endothelial cells. The Osp-less mutant was unable to evoke a detectable immune response after intradermal live cell immunization even though mutant survived in the skin the same duration as wild-type cells. Polyclonal mouse serum raised against Osp-less cells inhibited growth of the mutant but not of wild-type cells, an indication that other antigens are present on the surface of the Osp-less mutant. Two different classes, A and B, of monoclonal antibodies (mAb) with growth inhibiting properties for mutant cells were produced. Class A mAbs bound to 13 kDa surface proteins of *B. burgdorferi* sensu stricto and of *B. afzelii*. The minimum inhibitory concentration of the Fab fragment of one mAb of this class was 0.2 .mu.g/ml. Class B mAbs did not bind by Western Blot to *B. burgdorferi* cells but reacted with cells in an unfixed cell immunofluorescence assay and growth inhibition assay. These studies revealed hitherto unknown functional aspects of Osp proteins, notably serum-resistance, and indicated that in the absence of Osp proteins other antigens are expressed or become accessible at the cell's surface.

AB All \*\*\**Borrelia*\*\*\* *burgdorferi* sensu lato isolates characterized to date have one or a combination of several major outer surface proteins (Osp). Mutants. . .

SUMM Lyme disease is a complex, multisystemic illness caused by at least three genomic species of the spirochete \*\*\**Borrelia*\*\*\* *burgdorferi* sensu lato (reviewed in Barbour and Fish, 1993). Virtually all North American isolates have been classified as *B. burgdorferi*. . . et al., 1992; Boerlin et al., 1992; Welsh et al., 1992). European isolates also include two other genomic species, *B. garinii*\*\*\* and *B. afzelii* (Baranton et al., 1992; Canica et al., 1993). The clinical features and epidemiology of Lyme disease have. . . characterized (reviewed review in Barbour and Fish, 1993). Comparatively less, however, is known about the pathogenic features of Lyme disease \*\*\**borrelia*\*\*\* and immunopathological responses to them in the host.

SUMM . . . basic information about all spirochetes. The spirochete cell is unique in several aspects (Holt, 1978). One of the features of

\*\*\**borrelia*\*\*\* is the abundance of one or several lipoproteins in the outer cell membrane (Bergstrom et al., 1989; Brandt et al.,. . . been learned about immunogenicity, as well as biochemical and genetic aspects, of these lipoproteins in Lyme disease and relapsing fever

\*\*\**borrelia*\*\*\* (Barbour, 1993; Bergstrom et al., 1989; Brandt et al., 1990; Johnson et al., 1992; Kitten and Barbour, 1990; Meier et. . .

SUMM The lipoproteins OspA and OspB are major contributors to antigenic distinctness of Lyme disease \*\*\*borrelia\*\*\* (Barbour and Fish, 1993). Both OspA and OspB are co-transcribed from a single operon located on linear plasmid of 49. . .

SUMM . . . The findings of Cadavid et al. indicated that differences in invasive properties and tissues tropism between serotypes of related spirochete \*\*\*Borrelia\*\*\* turicatae, a relapsing fever agent, may be determined by the expression of a single surface protein that is analogous to. . .

SUMM . . . al., 1992, Sadziene et al., 1993B). First the morphology and function of the Osp-less mutant were characterized to determine whether \*\*\*borrelia\*\*\* lacking OspA, B, C, and D would be altered in such functional properties, as (i) generation time, (ii) ability to. . . potential to evoke immune response after intradermal live cell inoculation, and (vi) ability to survive in the skin. Among pathogenic \*\*\*borrelia\*\*\* the role of surface lipoproteins in these respects have not yet been reported.

SUMM . . . showed the presence of a major low-molecular-weight lipoprotein specific for *B. burgdorferi* and raised the possibility that it was a \*\*\*borrelia\*\*\* equivalent of Braun's lipoprotein (Katona et al., 1992). Another study reported an immunogenic 14 kDa surface protein of *B. burgdorferi*. . .

DRWD FIG. 3A. Western blot analysis with antibody 15G6. *B. burgdorferi* B311 and B313, *B. afzelii* ACAI, *B. garinii*\*\*\* \*\*\*IP90\*\*\* and *B. hermsii* Bh33 were probed with the antibody 15G6 mAb.

DETD . . . al., 1988), both of which are *B. burgdorferi* sensu stricto, *B. afzelii* strain ACAI (Boerlin et al., 1992) and *B. garinii*\*\*\* strain \*\*\*Ip90\*\*\* (Baranton et al., 1992; Boerlin et al., 1992) (Table 1). *B. hermsii* HS1 serotype 33 (ATCC 35209; Barbour et al., 1982) was abbreviated to Bh33. \*\*\*Borrelia\*\*\* were grown in BSK II medium and harvested by methods described previously (Barbour, 1984; Barbour et al., 1983). When culturing. . . (25 .mu.g/ml) were added to the medium. Cells were counted in a Petroff-Hauser chamber by phase-contrast microscopy. In some studies \*\*\*borrelia\*\*\* were also grown on solid BSK II medium as described (Hinnebusch and Barbour, 1992; Sadziene et al., 1992). To estimate growth rate, \*\*\*borrelia\*\*\* at an initial concentration of 2.times.10.sup.6 cells/ml, were grown in tightly capped, 13.times.100-mm polystyrene culture tubes (Falcon Labware, Lincoln Park, . . . final cell pellet was determined with Bradford reagent (Bio-Rad Laboratories, Richmond, Calif., (Barbour et al., 1983). The microscopic aggregation of \*\*\*borrelia\*\*\* alone or in the presence of antibodies was graded according to the following scale: 0, single cells with less than. . .

DETD . . . 1983

Sh.2 + + + - Schwan et al.,  
1988

*B. afzelii* ACAI + + + - Boerlin et al.,  
1992

*B. garinii*\*\*\* \*\*\*IP90\*\*\* + + + - Baranton et al.,  
1992; Boerlin et  
al., 1992

.sup.a Osp profile was determined by Western blot analysis.

DETD . . . mAb H4825 (Barbour et al., 1984) have been given. Monoclonal antibody H9724 binds to native and denatured flagellins of different \*\*\*Borrelia\*\*\* species (Barbour et al., 1986). These antibodies are

IgG subclass 2a (IgG2a).

DETD . . . antibodies were produced for this study. Female, 6-8 week old BALB/c mice (Jackson Laboratory, Bar Harbor, Ma.) were used. Freshly-harvested \*\*\*borrelia\*\*\* were washed with and resuspended in PBS, pH 7.0. The total cellular protein in the suspension was estimated with Bradford. . . the boost. After collection, sera were evaluated by ELISA and GIA. On day 52, the mice received intravenously 2.times.10.sup.8 viable \*\*\*borrelia\*\*\* in 100 .mu.l of PBS. Fusion of mouse splenocytes with NS1 myeloma cells were performed on day 56 by a . . .

DETD The method for ELISA was essentially as described previously (Sadziene et al., 1991). For this "dry" ELISA \*\*\*borrelia\*\*\* at a total protein concentration of 1.4 .mu.g/ml in phosphate-buffered saline (PBS), pH 7.0 were dried onto polystyrene 96-well microtiter plates at 37.degree. C. for 18 h. For a "wet" ELISA \*\*\*borrelia\*\*\* at a total protein concentration of 3 .mu.g/ml in 15 mM Na.sub.2 CO.sub.3 -35 mM NaHCO.sub.3 buffer, pH 9.6 were. . .

DETD . . . assay (IFA) of fixed, dried cells was performed as described (Barbour et al., 1982; Barbour et al., 1983). Harvested, fresh \*\*\*borrelia\*\*\* were washed with RPMI 1640 medium, mixed with a suspension of washed rat erythrocytes in 50% RPMI 1640-50% fetal calf.

DETD . . . of mAb to unfixed live spirochetes was assessed by a modification of the described procedure (Barbour et al., 1983). 10.sup.7 \*\*\*borrelia\*\*\* were washed with 2% (wt/vol) BSA in PBS/Mg (PBS/Mg/BSA) and then resuspended in 0.5 ml of undiluted hybridoma culture supernatant. . .

DETD . . . mixed together, dialyzed in the dark against PBS for 24 h, and concentrated with a Centriprep RTM.-10 (Amicon, Beverly, Mass.). 10.sup.7 \*\*\*borrelia\*\*\* in log-phase growth were resuspended in RPMI 1640 medium with 10-100 .mu.g/ml of antibody-fluorescein conjugate and examined for fluorescence at. . .

DETD . . . assay (GIA) was described previously (Sadziene et al., 1993C). Briefly, to a 100 .mu.l volume of BSK II containing 2.times.10.sup.6 \*\*\*borrelia\*\*\* was added an equal volume of heat-activated (56.degree. C. for 30 min) mAb or polyclonal antiserum, serially diluted two-fold in BSK II. To evaluate the susceptibility of \*\*\*borrelia\*\*\* to fresh, nonimmune serum, the same growth inhibition technique was applied using pooled unheated serum from C3H/HeN mice (Taconic, Germantown, . . . immediately frozen at -135.degree. C. Heat-inactivated serum from the same mice served as a control. To determine the susceptibility of \*\*\*borrelia\*\*\* to complement, unheated or heated (56.degree. C. for 30 min) guinea pig complement (Diamedix, Miami, Fla.) was added to each. . .

DETD . . . 17% acrylamide as described previously (Barbour, 1984; Barbour et al., 1982). In some experiments, cleavage of surface-exposed proteins of intact \*\*\*borrelia\*\*\* with proteinase K (Boehringer-Mannheim) was carried out (Sadziene et al., 1992). For this study 490 .mu.l of a suspension containing. . .

DETD An assay for adherence of intrinsically-labeled \*\*\*borrelia\*\*\* to human umbilical vein endothelium (HUVE) cells was carried out essentially as described (Thomas and Comstock, 1989). Briefly, \*\*\*borrelia\*\*\* were intrinsically radiolabeled with [.sup.35 S]-methionine, washed with PBS and resuspended to a density of 1.7.times.10.sup.8 cells per ml in. . . ICN Pharmaceuticals, Irvine,

Calif.), and counted by scintillation. The assay was done with triplicate samples and performed twice. Differences between \*\*\*borrelia\*\*\* populations in adhesion were analyzed by Student's t test.

DETD Six-to-eight week old, female C3H/HeN mice (Taconic, Germantown, N.Y.) were used. \*\*\*Borrelia\*\*\* were counted and diluted in BSK II to give the desired inoculum. For live cell immunization, 10 .mu.l of cells. . . of cultivation; they were scored as negative when no motile spirochetes were seen in forty 400.times. fields. For evaluation of \*\*\*borrelia\*\*\* survival in skin, \*\*\*borrelia\*\*\* were diluted in 1X BSK II. The abdominal skin was shaved, and 10.sup.7

\*\*\*borrelia\*\*\* cells were injected intradermally at 3 or 4 separate locations. Mice were sacrificed at 0.25, 0.5, 2, 6, 9, 12,. . .

DETD . . . phase. One possible explanation for this is that metabolic activity of the Osp-less mutant was lower than that of wild-type \*\*\*borrelia\*\*\*. Alternatively, the OspA.sup.- OspB.sup.- mutant may have a slower rate of growth than its parent B311 and, consequently, does not reach the same cell densities as wild-type \*\*\*borrelia\*\*\* at a particular time point. To examine these possibilities the growth rates of B311 and B313 were determined and the amount of \*\*\*borrelia\*\*\* protein in the final cell pellet was measured.

DETD This study was performed twice, each time plating in triplicate 10.sup.1 -10.sup.6 \*\*\*borrelia\*\*\* per plate. B311 cells grew as colonies with the expected plating efficiency of 50%. The efficiency of B313 plating was. . .

DETD . . . burgdorferi B311 and B313 cells to HUVE cell monolayers was measured after 4 h at 4.degree. C. At this temperature \*\*\*borrelia\*\*\* do not detectably enter endothelial cells and adherence of cells becomes maximal by 4 h (Comstock and Thomas, 1989). The. . . in Table 2. The ability of Osp-less cells to adhere HUVE monolayer both times was only half that of wild-type \*\*\*borrelia\*\*\*, a difference that was significant ( $P<0.001$ ).

DETD . . . in spite of classical and alternative complement pathway activation (Kochi and Johnson, 1987). It was determined whether or not the \*\*\*borrelia\*\*\*'s ability to resist the nonspecific bactericidal effects of complement might be attributable to Osp proteins. Accordingly, B311 cells and the. . . was observed at the lowest serum dilution of 1:8. In contrast, the minimum inhibitory titer of nonimmune serum against Osp-less \*\*\*borrelia\*\*\* was 1:64. In wells with inhibited growth the B313 cells were nonmotile and had large

DETD . . . 4.degree. C.

.sup.c Radioactivity bound to host cells following incubation and washing, expressed as the mean of three samples.

.sup.d Differences between \*\*\*borrelia\*\*\* populations in adhesion were analyzed by a Student's t test ( $P < 0.001$ ).

DETD Survival of \*\*\*Borrelia\*\*\* in Skin

DETD In the previous study it was shown that outer surface lipoproteins might have a role in protecting \*\*\*borrelia\*\*\* from one nonspecific host defense, namely, complement. \*\*\*Borrelia\*\*\* invade the host through the skin, being able to survive in it from a few days to years (Steere, 1989). Accordingly, it was evaluated whether Osp proteins might also protect \*\*\*borrelia\*\*\* from nonspecific resistance factors in the skin of the mouse., (e.g., different chemical substances from tissues with antibacterial activity, early. . .

DETD . . . from 18 and 24 h after inoculation was positive. These findings

indicated that OspA and/or OspB might not benefit the \*\*\*borrelia\*\*\* survival in the skin. To confirm that cells that survived in the skin retained the same phenotype, 6 randomly chosen. . .

DETD . . . with live B313 before the spleen fusion. As a screen for surface-directed mAbs, an ELISA was used in which whole \*\*\*borrelia\*\*\* were not dried in the microtiter plate wells. To further evaluate mAbs for surface binding all hybridoma supernatants identified by. . .

DETD . . . it was determined whether 15G6 or 7D4 mAbs recognized similar or identical proteins in other genomic species of Lyme disease \*\*\*borrelia\*\*\*. The results with 15G6 are shown in FIG. 3; the same results were obtained with 7D4. Representatives of *B. afzelii* and *B. hermsii* cells by Western blot. The mAb recognized a. . . protein of slightly higher apparent molecular weight in *B. afzelii* ACAI. Neither 15G6 nor 7D4 recognized any protein in *B. garinii* \*\*\*IP90\*\*\* or *B. hermsii*.

DETD . . . to 15G6 mAb by the Western blot in the whole-cell lysates, it was not recognized in the dried and fixed \*\*\*borrelia\*\*\*.

DETD The binding of fluorescein-labeled antibodies to fixed and unfixed \*\*\*borrelia\*\*\* were assessed. B313 cells were examined at 3, 15, 30, 60, and 360 min after addition of the 15G6 conjugate. . .

DETD sensu lato and the other genomic species of Lyme disease agents. Other isolates of Lyme disease \*\*\*borrelia\*\*\* have one or more of the Osp proteins (reviewed in Barbour and Fish, 1993). The study showed that the Osp-less. . .

DETD . . . of *B. burgdorferi* sensu lato also have a poor plating efficiency on solid medium. The diminished ability of aggregated Osp-less \*\*\*borrelia\*\*\* to move about the broth medium may explain their slower growth under that condition, but why B313 cells could not.

DETD . . . adhere to human endothelial cells. This indicates that the phenomenon of self-aggregation is not equivalent to the association of the \*\*\*borrelia\*\*\* with mammalian cells. Prior studies had revealed functions for OspA in endothelial cell adherence and for OspB in cell penetration. . . The findings of the present study are also consistent with a role for OspA and/or OspB in the association of \*\*\*borrelia\*\*\* with mammalian cells.

DETD . . . is known about what confers "serum-resistance" to Gram-negative and Gram-positive bacteria; less is known about this aspect of spirochetes. Although \*\*\*borrelia\*\*\* have two membranes sandwiching a peptidoglycan layer, as do Gram-negative bacteria, the outer membrane of \*\*\*borrelia\*\*\* appears to be more fluid than that of Gram-negative bacteria (Barbour and Hayes, 1986) and lack lipid A-containing glycolipids (Takayama. . . suggest that OspA and/or OspB protect the cells from complement attack. When OspA, B, C, and D are lacking, the \*\*\*borrelia\*\*\* were more susceptible than OspA.sup.+ B.sup.+ cells to unheated, nonimmune serum and to guinea pig complement.

DETD Whatever protection OspA and OspB appeared to confer to the \*\*\*borrelia\*\*\* in serum did not seem to provide an advantage to cells in skin. In these studies two isolates were used. . .

DETD . . . B311 and B313 with respect to skin survival, one might expect that the immune responses to intradermal inoculation of viable \*\*\*borrelia\*\*\* would be comparable. Although the Osp-less mutant lacked two proteins, OspA and OspB, that are immunodominant when syringe

inocula of . . .

DETD . . . another the Osp proteins. A slightly larger protein recognized by the mAb was present in a *B. afzelii* strain. If \*\*\*Ip90\*\*\* , a representative of *B. garinii*\*\*\* , have a homologous protein it does not share the mAbs' epitope.

DETD . . . of *B. burgdorferi* was reported (Sambri et al., 1991). This was identified with a mAb and by immunofluorescence of live \*\*\*borrelia\*\*\* . In contrast with what was observed with mAbs to p13 and with antibody to the 10 kDa protein (Habicht, 1993), . . .

DETD The effect of 15G6 on susceptible \*\*\*borrelia\*\*\* was similar to what was observed with the anti-OspB mAb H6831 (Sadziene et al., 1994). Binding to the cells was . . .

DETD These results also provide evidence of the interaction of antibodies and \*\*\*borrelia\*\*\* and, in particular, those lacking the known Osp proteins. The target or targets for the second class of mAbs remains. . .

DETD Baranton, G. et al., "Delineation of \*\*\**Borrelia*\*\*\* *burgdorferi* sensu stricto, \*\*\**Borrelia*\*\*\* \*\*\**garinii*\*\*\* sp.nov., and group VS461 associated with Lyme \*\*\*borreliosis\*\*\* , " Int. J. Syst. Bacteriol., 42:378-383, 1992.

DETD Barbour, A. G., "Linear DNA or \*\*\**Borrelia*\*\*\* species and antigenic variation," Trends in Microbiology, 1:236-239, 1993.

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DETD Barbour, A. G. and Hayes, S. F., "Biology of \*\*\**Borrelia*\*\*\* species," Microbiol. Rev., 50:381-400, 1986.

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DETD Barbour, A. G. et al., "Variable major proteins of \*\*\**Borrelia*\*\*\* *hermsii*," J. Exp. Med., 156:1312-1324, 1982.

DETD Barthold, S. W. and Bockenstedt, L. K., "Passive immunizing activity of sera from mice infected with \*\*\**Borrelia*\*\*\* *burgdorferi*," Infect. Immun., 61:4696-4702, 1993.

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CLM What is claimed is:

... determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS/PAGE), that binds to the monoclonal antibody 15G6 and is isolatable from \*\*\*Borrelia\*\*\* burgdorferi.

2. The protein composition of claim 1, wherein the composition further consists essentially of \*\*\*Borrelia\*\*\* burgdorferi outer membrane

proteins OspA, OspB, OspC or OspD.

3. An isolated protein having the following characteristics: (a) isolatable from \*\*\**Borrelia*\*\*\* burgdorferi; (b) present on the surface of \*\*\**Borrelia*\*\*\* burgdorferi cells that lack the outer membrane proteins OspA, OspB, OspC and OspD; (c) sensitive to cleavage with proteinase K; . . .
4. The isolated protein of claim 3, further defined as being obtained from \*\*\**Borrelia*\*\*\* burgdorferi cells.
5. An isolated protein characterized as: isolatable from \*\*\**Borrelia*\*\*\* burgdorferi; having a molecular weight of about 13 kDa, as determined by SDS/PAGE; and binding to monoclonal antibody 15G6.
8. A method for detecting antibodies to \*\*\**Borrelia*\*\*\* burgdorferi comprising contacting a sample suspected of containing antibodies to \*\*\**Borrelia*\*\*\* burgdorferi with a protein as claimed in claim 5 under antibody-binding conditions and detecting any antibody binding to the protein, whereby antibody binding to the protein is indicative of the presence of antibodies to \*\*\**Borrelia*\*\*\* burgdorferi.
10. The method of claim 9 wherein the pharmaceutically acceptable composition further comprises \*\*\**Borrelia*\*\*\* burgdorferi OspA, OspB, OspC or OspD.

L15 ANSWER 5 OF 21 USPATFULL

AN 2001:167742 USPATFULL

TI Methods and compositions including a 13kDa B. burgdorferi protein

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PI US 6296849 B1 20011002

AI US 1999-412060 19991004 (9)

RLI Division of Ser. No. US 1994-264036, filed on 22 Jun 1994

DT Utility

FS GRANTED

EXNAM Primary Examiner: Swartz, Rodney P.

LREP Frommer Lawrence & Haug, Kowalski, Thomas J.

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN 12 Drawing Figure(s); 5 Drawing Page(s)

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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB All \*\*\**Borrelia*\*\*\* burgdorferi sensu lato isolates characterized to date have one or a combination of several major outer surface proteins (Osp). Mutants of B. burgdorferi lacking Osp proteins were selected with polyclonal or monoclonal antibodies at a frequency of 10.sup.-6 to 10.sup.-5. One mutant that lacked OspA, B, C and D was further characterized in the present study. It was distinguished from the OspA.sup.+ B.sup.+ cells by its (i) auto-aggregation and slower growth rate, (ii) decreased plating efficiency on solid medium, (iii) serum- and complement-sensitivity, and (iv) diminished capacity to adhere to human umbilical vein endothelial cells. The Osp-less mutant was unable

to evoke a detectable immune response after intradermal live cell immunization even though mutant survived in the skin the same duration as wild-type cells. Polyclonal mouse serum raised against Osp-less cells inhibited growth of the mutant but not of wild-type cells, an indication that other antigens are present on the surface of the Osp-less mutant. Two different classes, A and B, of monoclonal antibodies (mAb) with growth inhibiting properties for mutant cells were produced. Class A mAbs bound to 13 kDa surface proteins of *B. burgdorferi* sensu stricto and of *B. afzelii*. The minimum inhibitory concentration of the Fab fragment of one mAb of this class was 0.2 .mu.g/ml. Class B mAbs did not bind by Western blot to *B. burgdorferi* cells but reacted with cells in an unfixed cell immunofluorescence assay and growth inhibition assay. These studies revealed hitherto unknown functional aspects of Osp proteins, notably serum-resistance, and indicated that in the absence of Osp proteins other antigens are expressed or become accessible at the cell's surface.

AB All \*\*\**Borrelia*\*\*\* *burgdorferi* sensu lato isolates characterized to date have one or a combination of several major outer surface proteins (Osp). Mutants. . .

SUMM Lyme disease is a complex, multisystemic illness caused by at least three genomic species of the spirochete \*\*\**Borrelia*\*\*\* *burgdorferi* sensu lato (reviewed in Barbour and Fish, 1993). Virtually all North American isolates have been classified as *B. burgdorferi*. . . et al., 1992; Boerlin et al., 1992; Welsh et al., 1992). European isolates also include two other genomic species, *B. garinii*\*\*\* and *B. afzelii* (Baranton et al., 1992; Canica et al., 1993). The clinical features and epidemiology of Lyme disease have. . . characterized (reviewed review in Barbour and Fish, 1993). Comparatively less, however, is known about the pathogenic features of Lyme disease \*\*\**borrelia*\*\*\* and immunopathological responses to them in the host.

SUMM . . . basic information about all spirochetes. The spirochete cell is unique in several aspects (Holt, 1978). One of the features of

\*\*\**borrelia*\*\*\* is the abundance of one or several lipoproteins in the outer cell membrane (Bergstrom et al., 1989; Brandt et al., . . . been learned about immunogenicity, as well as biochemical and genetic aspects, of these lipoproteins in Lyme disease and relapsing fever

\*\*\**borrelia*\*\*\* (Barbour, 1993; Bergstrom et al., 1989; Brandt et al., 1990; Johnson et al., 1992; Kitten and Barbour, 25 1990; Meier. . .

SUMM The lipoproteins OspA and OspB are major contributors to antigenic distinctness of Lyme disease \*\*\**borrelia*\*\*\* (Barbour and Fish, 1993). Both OspA and OspB are co-transcribed from a single operon located on linear plasmid of 49. . .

SUMM . . . The findings of Cadavid et al. indicated that differences in invasive properties and tissues tropism between serotypes of related spirochete \*\*\**Borrelia*\*\*\* turicatae, a relapsing fever agent, may be determined by the expression of a single surface protein that is analogous to. . .

SUMM . . . al., 1992, Sadziene et al., 1993B). First the morphology and function of the Osp-less mutant were characterized to determine whether \*\*\**borrelia*\*\*\* lacking OspA, B, C, and D would be altered in such functional properties, as (i) generation time, (ii) ability to. . . potential to evoke immune response after intradermal live cell inoculation, and (vi) ability to survive in the skin. Among pathogenic \*\*\**borrelia*\*\*\* the role of surface lipoproteins in these respects have not yet been reported.

SUMM . . . showed the presence of a major low-molecular-weight lipoprotein specific for *B. burgdorferi* and raised the possibility that it was a \*\*\*borrelial\*\*\* equivalent of Braun's lipoprotein (Katona et al., 1992). Another study reported an immunogenic 14 kDa surface protein of *B. burgdorferi*. . .

DRWD FIG. 3A. Western blot analysis with antibody 15G6. *B. burgdorferi* B311 and B313, *B. afzelii* ACAI, *B. garinii* \*\*\*IP90\*\*\* and *B. hermsii* Bh33 were probed with the antibody 15G6 mAb.

DETD . . . both of which are *B. burgdorferi* sensu stricto, *B. afzelii* strain ACAI (Boerlin et al., 1992) and *B. garinji* strain \*\*\*Ip90\*\*\* (Baranton et al., 1992; Boerlin et al., 1992) (Table 1). *B. hermsii* HS1 serotype 33 (ATCC 35209; Barbour et al., 1982) was abbreviated to Bh33.

\*\*\*Borrelia\*\*\* were grown in BSK II medium and harvested by methods described previously (Barbour, 1984; Barbour et al., 1983). When culturing. . . (25 .mu.g/ml) were added to the medium. Cells were counted in a Petroff-Hauser chamber by phase-contrast microscopy. In some studies \*\*\*borrelia\*\*\* were also grown on solid BSK II medium as described (Hinnebusch and Barbour, 1992; Sadziene et al., 1992). To estimate growth rate, \*\*\*borrelia\*\*\* at an initial concentration of 2.times.10.sup.6 cells/ml, were grown in tightly capped, 13.times.100-mm polystyrene culture tubes (Falcon Labware, Lincoln Park, . . . final cell pellet was determined with Bradford reagent (Bio-Rad Laboratories, Richmond, Calif., (Barbour et al., 1983). The microscopic aggregation of \*\*\*borrelia\*\*\* alone or in the presence of antibodies was graded according to the following scale: 0, single cells with less than. . .

DETD . . . 1983

Sh.2 + + - Schwan

et al., 1988

*B. afzelii* ACAI + + - Boerlin

et al., 1992

*B. garinii* \*\*\*IP90\*\*\* + + - Baranton

et al., 1992;

Boerlin

et al., 1992

.sup.a Osp profile was determined by Western blot analysis.

DETD . . . mAb H4825 (Barbour et al., 1984) have been given. Monoclonal antibody H9724 binds to native and denatured flagellins of different \*\*\*Borrelia\*\*\* species (Barbour et al., 1986). These antibodies are IgG subclass 2a (IgG2a).

DETD . . . antibodies were produced for this study. Female, 6-8 week old BALB/c mice (Jackson Laboratory, Bar Harbor, Me.) were used. Freshly-harvested \*\*\*borrelia\*\*\* were washed with and resuspended in PBS, pH 7.0. The total cellular protein in the suspension was estimated with Bradford. . . the boost. After collection, sera were evaluated by ELISA and GIA. On day 52, the mice received intravenously 2.times.10.sup.1 viable \*\*\*borrelia\*\*\* in 100 .mu.l of PBS. Fusion of mouse splenocytes with NS1 myeloma cells were performed on day 56 by a. . .

DETD The method for ELISA was essentially as described previously (Sadziene et al., 1991). For this "dry" ELISA \*\*\*borrelia\*\*\* at a total protein concentration of 1.4 .mu.g/ml in phosphate-buffered saline (PBS), pH 7.0 were dried onto polystyrene 96-well microtiter plates at 37.degree. C. for 18 h. For a "wet" ELISA \*\*\*borrelia\*\*\* at a total protein concentration of 3 .mu.g/ml in 15 mM Na.sub.2 CO.sub.3 -35 mM NaHCO.sub.3 buffer, pH 9.6 were. . .

DETD . . . assay (IFA) of fixed, dried cells was performed as described (Barbour et al., 1982; Barbour et al., 1983). Harvested, fresh \*\*\*borrelia\*\*\* were washed with RPMI 1640 medium, mixed with a suspension of washed rat erythrocytes in 50% RPMI 1640-50% fetal calf.

DETD . . . of mAb to unfixed live spirochetes was assessed by a modification of the described procedure (Barbour et al., 1983). 10.sup.7 \*\*\*borrelia\*\*\* were washed with 2% (wt/vol) BSA in PBS/Mg (PBS/Mg/BSA) and then resuspended in 0.5 ml of undiluted hybridoma culture supernatant. . .

DETD . . . mixed together, dialyzed in the dark against PBS for 24 h, and concentrated with a Centriprep RTM.-10 (Amicon, Beverly, Mass.). 10<sup>7</sup> \*\*\*borrelia\*\*\* in log-phase growth were resuspended in RPMI 1640 medium with 10-100 .mu.g/ml of antibody-fluorescein conjugate and examined for fluorescence at. . .

DETD . . . assay (GIA) was described previously (Sadziene et al., 1993C). Briefly, to a 100 .mu.l volume of BSK II containing 2.times.10.sup.6 \*\*\*borrelia\*\*\* was added an equal volume of heat-activated (56.degree. C. for 30 min) mAb or polyclonal antiserum, serially diluted two-fold in BSK II. To evaluate the susceptibility of \*\*\*borrelia\*\*\* to fresh, nonimmune serum, the same growth inhibition technique was applied using pooled unheated serum from C3H/HeN mice (Taconic, Germantown, . . . immediately frozen at -135.degree. C.

Heat-inactivated serum from the same mice served as a control. To determine the susceptibility of \*\*\*borrelia\*\*\* to complement, unheated or heated (56.degree. C. for 30 min) guinea pig complement (Diamedix, Miami, Fla.) was added to each. . .

DETD . . . 17% acrylamide as described previously (Barbour, 1984; Barbour et al., 1982). In some experiments, cleavage of surface-exposed proteins of intact \*\*\*borrelia\*\*\* with proteinase K (Boehringer-Mannheim) was carried out (Sadziene et al., 1992). For this study 490 .mu.l of a suspension containing. . .

DETD An assay for adherence of intrinsically-labeled \*\*\*borrelia\*\*\* to human umbilical vein endothelium (HUVE) cells was carried out essentially as described (Thomas and Comstock, 1989). Briefly, \*\*\*borrelia\*\*\* were intrinsically radiolabeled with [.sup.35 S]-methionine, washed with PBS and resuspended to a density of 1.7.times.10.sup.8 cells per ml in. . . ICN Pharmaceuticals, Irvine, Calif.), and counted by scintillation. The assay was done with triplicate samples and performed twice. Differences between \*\*\*borrelia\*\*\* populations in adhesion were analyzed by Student's t test.

DETD Six-to-eight week old, female C3H/HeN mice (Taconic, Germantown, N.Y.) were used. \*\*\*Borrelia\*\*\* were counted and diluted in BSK II to give the desired inoculum. For live cell immunization, 10 .mu.l of cells. . . of cultivation; they were scored as negative when no motile spirochetes were seen in forty 400.times. fields. For evaluation of \*\*\*borrelia\*\*\* survival in skin, \*\*\*borrelia\*\*\* were diluted in 1.times.BSK II. The abdominal skin was shaved, and 10.sup.7 \*\*\*borrelia\*\*\* cells were injected intradermally at 3 or 4 separate locations. Mice were sacrificed at 0.25, 0.5, 2, 6, 9, 12,. . .

DETD . . . phase. One possible explanation for this is that metabolic activity of the Osp-less mutant was lower than that of wild-type \*\*\*borrelia\*\*\*. Alternatively, the OspA.sup.- OspB.sup.- mutant may have a slower rate of growth than its parent B311 and, consequently,

does not reach the same cell densities as wild-type \*\*\*borrelia\*\*\* at a particular time point. To examine these possibilities the growth rates of B311 and B313 were determined and the amount of \*\*\*borrelia\*\*\* protein in the final cell pellet was measured.

DETD This study was performed twice, each time plating in triplicate 10.sup.1 -10.sup.6 \*\*\*borrelia\*\*\* per plate. B311 cells grew as colonies with the expected plating efficiency of 50%. The efficiency of B313 plating was. . .

DETD . . . burgdorferi B311 and B313 cells to HUVE cell monolayers was measured after 4 h at 4.degree. C. At this temperature \*\*\*borrelia\*\*\* do not detectably enter endothelial cells and adherence of cells becomes maximal by 4 h (Comstock and Thomas, 1989). The. . . in Table 2. The ability of Osp-less cells to adhere HUVE monolayer both times was only half that of wild-type \*\*\*borrelia\*\*\*, a difference that was significant ( $P < 0.001$ ).

DETD . . . in spite of classical and alternative complement pathway activation (Kochi and Johnson, 1987). It was determined whether or not the \*\*\*borrelia\*\*\*'s ability to resist the nonspecific bactericidal effects of complement might be attributable to Osp proteins. Accordingly, B311 cells and the. . . was observed at the lowest serum dilution of 1:8. In contrast, the minimum inhibitory titer of nonimmune serum against Osp-less \*\*\*borrelia\*\*\* was 1:64. In wells with inhibited growth the B313 cells were nonmotile and had large membrane blebs. When heat-inactivated serum. . .

DETD . . . 4.degree. C.

.sup.c Radioactivity bound to host cells following incubation and washing, expressed as the mean of three samples.

.sup.d Differences between \*\*\*borrelia\*\*\* populations in adhesion were analyzed by a Student's t test ( $P < 0.001$ )

DETD Survival of \*\*\*Borrelia\*\*\* in Skin

DETD In the previous study it was shown that outer surface lipoproteins might have a role in protecting \*\*\*borrelia\*\*\* from one nonspecific host defense, namely, complement. \*\*\*Borrelia\*\*\* invade the host through the skin, being able to survive in it from a few days to years (Steere, 1989). Accordingly, it was evaluated whether Osp proteins might also protect \*\*\*borrelia\*\*\* from nonspecific resistance factors in the skin of the mouse., (e.g., different chemical substances from tissues with antibacterial activity, early. . .

DETD . . . from 18 and 24 h after inoculation was positive. These findings indicated that OspA and/or OspB might not benefit the \*\*\*borrelia\*\*\*'s survival in the skin. To confirm that cells that survived in the skin retained the same phenotype, 6 randomly chosen. . .

DETD . . . with live B313 before the spleen fusion. As a screen for surface-directed mAbs, an ELISA was used in which whole \*\*\*borrelia\*\*\* were not dried in the microtiter plate wells. To further evaluate mAbs for surface binding all hybridoma supernatants identified by. . .

DETD . . . it was determined whether 15G6 or 7D4 mAbs recognized similar or identical proteins in other genomic species of Lyme disease \*\*\*borrelia\*\*\*. The results with 15G6 are shown in FIG. 3; the same results were obtained with 7D4. Representatives of *B. afzelii* and *B. garinii* were evaluated at the same time as B311, B313 and *B. hermsii* cells by Western blot. The mAb recognized a. . . protein of slightly higher apparent molecular weight in *B. afzelii* ACAI. Neither 15G6 nor 7D4 recognized any protein in *B. garinii* \*\*\*IP90\*\*\*

or *B. hermsii*.

DETD . . . to 15G6 mAb by the Western blot in the whole-cell lysates, it was not recognized in the dried and fixed \*\*\*borrelia\*\*\*.

DETD The binding of fluorescein-labeled antibodies to fixed and unfixed \*\*\*borrelia\*\*\* were assessed. B313 cells were examined at 3, 15, 30, 60, and 360 min after addition of the 15G6 conjugate. . .

DETD . . . strains of *B. burgdorferi* sensu lato and the other genomic species of Lyme disease agents. Other isolates of Lyme disease \*\*\*borrelia\*\*\* have one or more of the Osp proteins (reviewed in Barbour and Fish, 1993). The study showed that the Osp-less. . .

DETD . . . of *B. burgdorferi* sensu lato also have a poor plating efficiency on solid medium. The diminished ability of aggregated Osp-less \*\*\*borrelia\*\*\* to move about the broth medium may explain their slower growth under that condition, but why B313 cells could not.

DETD . . . adhere to human endothelial cells. This indicates that the phenomenon of self-aggregation is not equivalent to the association of the \*\*\*borrelia\*\*\* with mammalian cells. Prior studies had revealed functions for OspA in endothelial cell adherence and for OspB in cell penetration. . . The findings of the present study are also consistent with a role for OspA and/or OspB in the association of \*\*\*borrelia\*\*\* with mammalian cells.

DETD . . . is known about what confers "serum-resistance" to Gram-negative and Gram-positive bacteria; less is known about this aspect of spirochetes. Although \*\*\*borrelia\*\*\* have two membranes sandwiching a peptidoglycan layer, as do Gram-negative bacteria, the outer membrane of \*\*\*borrelia\*\*\* appears to be more fluid than that of Gram-negative bacteria (Barbour and Hayes, 1986) and lack lipid A-containing glycolipids (Takayama. . . suggest that OspA and/or OspB protect the cells from complement attack. When OspA, B, C, and D are lacking, the \*\*\*borrelia\*\*\* were more susceptible than OspA+B+cells to unheated, nonimmune serum and to guinea pig complement.

DETD Whatever protection OspA and OspB appeared to confer to the \*\*\*borrelia\*\*\* in serum did not seem to provide an advantage to cells in skin. In these studies two isolates were used. . .

DETD . . . B311 and B313 with respect to skin survival, one might expect that the immune responses to intradermal inoculation of viable \*\*\*borrelia\*\*\* would be comparable. Although the Osp-less mutant lacked two proteins, OspA and OspB, that are immunodominant when syringe inocula of. . .

DETD . . . another the Osp proteins. A slightly larger protein recognized by the mAb was present in a *B. afzelii* strain. If \*\*\*Ip90\*\*\*, a representative of *B. garinii*\*\*\*, have a homologous protein it does not share the mAbs' epitope.

DETD . . . of *B. burgdorferi* was reported (Sambri et al., 1991). This was identified with a mAb and by immunofluorescence of live \*\*\*borrelia\*\*\*. In contrast with what was observed with mAbs to p13 and with antibody to the 10 kDa protein (Habicht, 1993),. . .

DETD The effect of 15G6 on susceptible \*\*\*borrelia\*\*\* was similar to what was observed with the anti-OspB mAb H6831 (Sadziene et al., 1994). Binding to the cells was. . .

DETD These results also provide evidence of the interaction of antibodies and \*\*\*borrelia\*\*\* and, in particular, those lacking the known osp proteins. The target or targets for the second class of mAbs remains. . .

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DETD Barthold, S. W. et al., "Kinetics of \*\*\*Borrelia\*\*\* burgdorferi dissemination and evolution of disease after intradermal inoculation of mice," Am. J. Pathol., 139:263-272, 1991.

DETD Benach, J. L. et al., "Biological activity of \*\*\*Borrelia\*\*\* burgdorferi antigens," Ann. NY Acad. Sci., 539:115-125, 1988.

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DETD Boerlin, P. et al., "Population genetic analysis of \*\*\*Borrelia\*\*\* burgdorferi isolates by multilocus enzyme electrophoresis," Infect. Immun., 60:1677-1683, 1992.

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DETD Hinnebush, J. and Barbour, A. G., "Linear- and circular-plasmid copy numbers in \*\*\*Borrelia\*\*\* burgdorferi," *J. Bacteriol.*, 174:5251-5257, 1992.

DETD Jonsson, M. et al., "Heterogeneity of outer membrane proteins in \*\*\*Borrelia\*\*\* burgdorferi: comparison of osp operons of three isolates of different geographic origins," *Infect. Immun.*, 60:1845-1853, 1992.

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DETD Kitten, T. and Barbour, A. G., "Juxtaposition of expressed variable antigen genes with a conserved telomere in the bacterium \*\*\*Borrelia\*\*\* hermsii," *Proc. Natl. Acad. Sci. USA*, 87:6077-6081, 1990.

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DETD Lam, T. T. et al., "Outer surface proteins E and F or \*\*\*Borrelia\*\*\* burgdorferi, the agent of Lyme disease," *Infect. Immun.*, 62:290-298, 1994.

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DETD Meier, J. et al., "Antigenic variation is associated with DNA rearrangement in a relapsing fever \*\*\*borrelia\*\*\*," *Cell*, 41:403-407, 1985.

DETD Norris, S. J. et al., "Low passage-associated proteins of \*\*\*Borrelia\*\*\* burgdorferi: characterization and molecular cloning of OspD, a surface-exposed, plasmid-encoded lipoprotein," *Infect. Immun.*, 60:4662-4672, 1992.

DETD Roehrig, J. T. et al., "The hamster immun response to tick-transmitted \*\*\*Borrelia\*\*\* burgdorferi differs from the response to needle-inoculated, cultured organisms," *J. Immunol.*, 149:3648-3653, 1992.

DETD Sadzicene, A. et al., "An OspB mutant of \*\*\*Borrelia\*\*\* burgdorferi has reduced invasiveness in vitro and reduced infectivity in vivo," *Infect. Immun.*, 61:3590-3596, 1993A.

DETD Sadzicene, A. et al., "A bactericidal antibody to \*\*\*Borrelia\*\*\* burgdorferi is directed against a variable region of the OspB protein," *Infect. Immun.*, in press, 1994.

DETD Sadzicene, A. et al., "Antibody-resistant mutants of \*\*\*Borrelia\*\*\* burgdorferi: in vitro selection and characterization," *J. Exp. Med.*,

176:799-809, 1992.

DETD Sadziene, A. et al., "A flagella-less mutant of \*\*\*Borrelia\*\*\* burgdorferi," J. Clin. Invest., 88:82-92, 1991.

DETD Sadziene, A. et al., "In vitro inhibition of \*\*\*Borrelia\*\*\* burgdorferi growth by antibodies," J. Infect. Dis., 167:165-172, 1993C.

DETD Sadziene, A. et al., "The cryptic OspC gene of \*\*\*Borrelia\*\*\* burgdorferi B31 is located on a circular plasmid," Infect. Immun., in press, 1993B.

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DETD Schwan, T. G. et al., "Changes in infectivity and plasmid profile of the Lyme disease spirochete, \*\*\*Borrelia\*\*\* burgdorferi, as a result of in vitro cultivation," Infect. Immun., 56:1831-1836, 1988.

DETD Simpson, W. J. et al., "Antibody to a 39-kilodalton \*\*\*Borrelia\*\*\* burgdorferi antigen (P39) as a marker for infection in experimentally and naturally inoculated animals," J. Clin. Microbiol., 29:236-243, 1991.

DETD Takayama, K. et al., "Absence of lipopolysaccharide in the Lyme disease spirochete, \*\*\*Borrelia\*\*\* burgdorferi," Infect. Immun., 55:2311-2313, 1987.

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DETD Wilske, B. et al., "Immunological and molecular polymorphism of OspC: an immunodominant major outer surface protein of \*\*\*Borrelia\*\*\* burgdorferi," Infect. Immun., 61:2182-2191, 1993.

CLM What is claimed is:

1. An isolated antibody that has binding affinity for an isolated protein having the following characteristics: (a) isolatable from \*\*\*Borrelia\*\*\* burgdorferi; (b) present on the surface of \*\*\*Borrelia\*\*\* burgdorferi cells that lack the outer membrane proteins OspA, OspB, OspC and OspD; (c) sensitive to cleavage with proteinase K;
5. An isolated antibody that has binding affinity for an isolated protein characterized as: isolatable from \*\*\*Borrelia\*\*\* burgdorferi; having a molecular weight of about 13 kDa, as determined by SDS/PAGE; and binding to monoclonal antibody 15G6.

L15 ANSWER 6 OF 21 USPATFULL

AN 2001:97430 USPATFULL

TI Immunological combination compositions and methods

IN Becker, Robert S., Henryville, PA, United States

Huebner, Robert C., Stroudsburg, PA, United States

Gray, Maryann B., Bartonsville, PA, United States

Biscardi, Karen S., South Sterling, PA, United States

PA Connaught Laboratories, Inc., Swiftwater, PA, United States (U.S. corporation)

PI US 6251405 B1 20010626

AI US 1995-476656 19950607 (8)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Swart, Rodney P.

LREP McDonnell Boehnen Hulbert & Berghoff

CLMN Number of Claims: 11

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 1274

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Immunological compositions and methods for making and using them. The compositions contain an antigen and a lipoprotein and optionally an adjuvant. The lipoprotein can itself be antigenic or immunoactive. The antigen can be influenza HA and the lipoprotein a recombinantly expressed product having an OspA leader for lipidation and PspA for the protein portion. The antigen can be OspC and the lipoprotein OspA. The components of the composition are co-administered. A potentiated immunological response is obtained by the compositions and methods.

PARN Reference, especially with respect to recombinant \*\*\*Borrelia\*\*\* proteins, is made to each of applications Ser. No. 07/973,338, filed Oct. 29, 1992; Ser. No. 08/373,455 (Rule 62 FWC. . .

SUMM . . . lipoprotein from expression of such aforementioned first and second nucleic acid sequences wherein the first nucleic acid sequence encodes a \*\*\*Borrelia\*\*\* lipoprotein leader sequence; preferably such a recombinant lipidated protein expressed using the nucleic acid sequence encoding the OspA leader sequence. . .

SUMM . . . majority of clinical isolates of *B. burgdorferi* from North America, a different picture has emerged from examination of the clinical \*\*\*Borrelia\*\*\* isolates in Europe. In Europe, Lyme disease is caused by three genospecies of \*\*\*Borrelia\*\*\*, namely *B. burgdorferi*, *B. garinii* and *B. afzelli*. In approximately half of the European isolates, OspA is not the most abundant outer surface protein. A. . .

SUMM . . . for a comparison of the ospA operons of three *B. burgdorferi* isolates of different geographic origins, namely B31, ACA1 and \*\*\*Ip90\*\*\*.

SUMM . . . would be useful to have a multivalent Lyme Disease immunological composition which contains antigens against both North American and European \*\*\*Borrelia\*\*\* isolates.

SUMM . . . in a host, animal or human. For instance, without wishing to necessarily limit the invention, the antigen can be: a \*\*\*Borrelia\*\*\* antigen, e.g., OspA, OspC, OspB, OspD; a pneumococcal antigen, e.g., PspA; an influenza (Flu) antigen such as HA; a pertussis. . .

SUMM . . . isolated from a suitable physiological source, or from an organism, e.g., bacteria; or can be recombinantly produced. Thus, the lipidated \*\*\*Borrelia\*\*\* antigens, e.g., recombinant OspA, and, the lipidated OspA and \*\*\*Borrelia\*\*\* fractions containing lipidated proteins (isolated by mild conditions) disclosed in the applications referenced in the Reference to Related Applications, and. . .

SUMM . . . except that the protein moiety is from expression of a ureA or ureB nucleic acid sequence); and OspC or another \*\*\*Borrelia\*\*\* antigen, or an influenza antigen, e.g., HA (such as from influenza A, e.g., Texas strain) as the antigen. Particular embodiments can include compositions: (i) comprising alum [adjuvant], OspA [lipoprotein] and another \*\*\*Borrelia\*\*\* antigen such as OspC [antigen]; (ii)

comprising alum [adjuvant], OspA [antigen], and OspA leader/OspC [lipoprotein]; (iii) comprising alum [adjuvant], OspA. . .

CLM What is claimed is:

1. An immunological composition comprising at least a first molecule and a second molecule, wherein the first molecule comprises \*\*\*Borrelia\*\*\* OspC antigen and the second molecule comprises an antigenic lipoprotein or lipopolypeptide selected from the group consisting of OspA, recombinant. . .
- . . . 9. The composition of claim 8 wherein said signal sequence is the signal sequence of an OspA protein of a \*\*\*Borrelia\*\*\* species, and the sequences are contiguous.
- . . . composition of claim 10 wherein in the hybrid nucleic acid molecule said mature protein is an OspC lipoprotein of a \*\*\*Borrelia\*\*\* species; or said mature protein is PspA.

L15 ANSWER 7 OF 21 USPATFULL

AN 2001:93350 USPATFULL

TI Chromosomally-encoded membrane protein of \*\*\*borrelia\*\*\* burgdorferi

IN Aron, Lieselotte, Hartsdale, NY, United States  
Cabello, Felipe, Hartsdale, NY, United States  
Godfrey, Henry P., Scarsdale, NY, United States  
Schwartz, Ira, Spring Valley, NY, United States

PA New York Medical College, Valhalla, NY, United States (U.S. corporation)

PI US 6248583 B1 20010619

AI US 1994-313412 19940927 (8)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Allen, Marianne P.

LREP Nixon Peabody LLP

CLMN Number of Claims: 8

ECL Exemplary Claim: 1

DRWN 4 Drawing Figure(s); 4 Drawing Page(s)

LN.CNT 1285

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to an isolated membrane protein or polypeptide encoded by chromosomal DNA of \*\*\*Borrelia\*\*\* burgdorferi (e.g., BmpC). This protein is encoded by a DNA molecule (e.g., bmpC) and is useful in vaccines to prevent infection by \*\*\*Borrelia\*\*\* burgdorferi, while antibodies raised against this protein can be employed in passively immunizing those already infected by the organism. Both these proteins and antibodies may be utilized in diagnostic assays to detect \*\*\*Borrelia\*\*\* burgdorferi and immune response in tissue or body fluids. Likewise, the DNA molecule can be used for detection of this organism.

TI Chromosomally-encoded membrane protein of \*\*\*borrelia\*\*\* burgdorferi

AB The present invention relates to an isolated membrane protein or polypeptide encoded by chromosomal DNA of \*\*\*Borrelia\*\*\* burgdorferi (e.g., BmpC). This protein is encoded by a DNA molecule (e.g., bmpC) and is useful in vaccines to prevent infection by \*\*\*Borrelia\*\*\* burgdorferi, while antibodies raised against this protein can be employed in passively immunizing those already infected by the organism. Both these proteins and antibodies may be utilized in diagnostic assays to detect \*\*\*Borrelia\*\*\* burgdorferi and immune response in tissue

or body fluids. Likewise, the DNA molecule can be used for detection of this. . .

SUMM The present invention relates to a chromosomally-encoded membrane protein or polypeptide of \*\*\*Borrelia\*\*\* burgdorferi.

SUMM . . . Lyme Disease and Babesiosis. Demonstration Of Spirochetes In The Myocardium," Ann. Inter. Med., 103:374-376 (1986); Syndman, D. R., et al., " \*\*\*Borrelia\*\*\* Burgdorferi In Joint Fluid In Chronic Lyme Arthritis," Ann. Inter. Med., 104:798-800 (1986)), the strong anti-B. burgdorferi cellular and humoral response in Lyme disease patients (Szczepanski, A., et al., "Lyme \*\*\*Borreliosis\*\*\* : Host Responses to \*\*\*Borrelia\*\*\* burgdorferi," Microbiol. Rev., 55:21-34-22 (1991); Rahn, D. W., "Lyme Disease: Clinical Manifestations, Diagnosis, and Treatment," Sem. Arthritis Rheum., 20:201-218 (1991)), . . . Ann. Inter. Med., 90:896-901 (1979)), heavy infiltration of the synovia of affected joints with T lymphocytes (Yssel, H., et al., " \*\*\*Borrelia\*\*\* Borgdorferi Activates a T Helper Type 1-Like T Cell Subset In Lyme Arthritis," J. Exp. Med., 174:593-601 (1991); Steere, A. . . Chronic Lyme Arthritis," Arthritis Rheum, 23:591-599 (1983)), histological similarities of Lyme disease arthritis and rheumatoid arthritis (Yssel, H., et al., " \*\*\*Borrelia\*\*\* Borgdorferi Activates a T Helper Type 1-Like T Cell Subset In Lyme Arthritis," J. Exp. Med., 174:593-601 (1991); Steere, A. . . Rheum, 23:591-599 (1983)), and cross-reactivity of B. burgdorferi antigens with human tissue (Fikrig, E., et al., "Serologic Response To The \*\*\*Borrelia\*\*\* Burgdorferi Flagellin Demonstrates An Epitope Common To A Neuroblastoma Cell Line," Proc. Natl. Acad. Sci. USA, 90:183-187 (1993)). B. burgdorferi. . . Antagonist And Recovery From Lyme Arthritis," Lancet, 341:146-148 (1993); Habicht, G. S., et al., "Cytokines And The Pathogenesis Of Neuroborreliosis: \*\*\*Borrelia\*\*\* Burgdorferi Induces Glioma Cells To Secrete Interleukin-6," J. Infect. Dis., 164:568-574 (1991). This could be important for Lyme disease pathogenesis. . .

SUMM . . . of genomic and antigenic similarities, and includes other non-classifiable strains (see Table I, below). Branton, G., et al., "Delineation of \*\*\*Borrelia\*\*\* Burgdorferi Sensu Stricto, \*\*\*Borrelia\*\*\* \*\*\*Garinii\*\*\* Sp. Nov., And Group VS461 Associated With Lyme \*\*\*Borreliosis\*\*\* , Int. J. Syst. Bacteriol, 42:378-383 (1992); Canica, M. M., et al., "Monoclonal Antibodies For Identification Of \*\*\*Borrelia\*\*\* Afzelii Sp. Nov. Associated With Late Cutaneous Manifestations Of Lyme \*\*\*Borreliosis\*\*\* , Scand. J. Infect. Dis., 25:441-448 (1993); Belfaiza, J., et al., "Genomic Fingerprinting of \*\*\*Borrelia\*\*\* Burgdorferi Sensu Lato By Pulse-Field Gel Electrophoresis," J. Clin. Microbiol., 31:2873-2877 (1993). B. burgdorferi sensu strictu consists only of genospecies I. Branton, G., et al., "Delineation of \*\*\*Borrelia\*\*\* Burgdorferi Sensu Stricto, \*\*\*Borrelia\*\*\* \*\*\*Garinii\*\*\* Sp. Nov., And Group VS461 Associated With Lyme \*\*\*Borreliosis\*\*\* , Int. J. Syst. Bacteriol, 42:378-383 (1992); Canica, M. M., et al., "Monoclonal Antibodies For Identification Of \*\*\*Borrelia\*\*\* Afzelii Sp. Nov. Associated With Late Cutaneous Manifestations Of Lyme \*\*\*Borreliosis\*\*\* , Scand. J. Infect. Dis., 25:441-448 (1993); Belfaiza, J., et al., "Genomic Fingerprinting of \*\*\*Borrelia\*\*\* Burgdorferi Sensu Lato By Pulse-Field Gel Electrophoresis," J. Clin. Microbiol., 31:2873-2877 (1993). In addition to antigenic variability between strains ((Szczepanski, A., et al., "Lyme \*\*\*Borreliosis\*\*\* : Host Responses To \*\*\*Borrelia\*\*\* Burgdorferi," Microbiol. Rev., 55:21-34-22 (1991); Barbour, A. G.,

"Biological And Social Determinants Of The Lyme Disease Problem," Infect. Agents Dis., . . . exposure to host defenses in a single host, and/or after repeated laboratory passages (Barbour, A. G., et al., "Biology Of \*\*\*Borrelia\*\*\* Species," Microbiol. Rev., 50:381-400 (1986)). The antigenic complexity of *B. burgdorferi* has in turn complicated development of vaccines and diagnostic. . .

SUMM . . . composed of a layer of carbohydrates covering an outer sheath or cell membrane. Barbour, A. G., et al., "Biology Of \*\*\*Borrelia\*\*\* Species," Microbiol. Rev., 50:381-400 (1986). This membrane is composed of a variety of proteins including OspA-E, a lipopolysaccharide, and a peptidoglycan. Barbour, A. G., et al., "Biology of \*\*\*Borrelia\*\*\* species," Microbiol. Rev., 50:381-400 (1986); Bergstrom, S., et al., "Molecular Analysis Of Linear Plasmid-encoded Major Surface Proteins, OspA and OspB, Of The Lyme Disease Spirochete \*\*\*Borrelia\*\*\* burgdorferi," Molec. Microbiol., 3:479-486 (1989); Fuchs, R., et al., "Molecular Analysis And Expression Of A \*\*\*Borrelia\*\*\* burgdorferi Gene Encoding A 22kDa Protein (pC) in Escherichia coli," Molec. Microbiol., 6:503-509 (1992); Lam, T. T., et al., "Outer Surface Proteins E and F of \*\*\*Borrelia\*\*\* burgdorferi, The Agent Of Lyme Disease," Infect. Immun., 62:290-298 (1994); Beck, G., et al., "Chemical And Biologic Characterization Of A Lipopolysaccharide From The Lyme Disease Spirochete ( \*\*\*Borrelia\*\*\* burgdorferi)," J. Infect. Dis., 152:108-117 (1985); Takayama, K., et al., "Absence of Lipopolysaccharide In The Lyme Disease Spirochete, \*\*\*Borrelia\*\*\* burgdorferi," Infect. Immun., 55:2311-2313 (1987). The existence of the latter two structures in *B. burgdorferi* is still controversial. Beck, G., et al., "Chemical And Biologic Characterization Of A Lipopolysaccharide From The Lyme Disease Spirochete ( \*\*\*Borrelia\*\*\* burgdorferi)," J. Infect. Dis., 152:108-117 (1985); Takayama, K., et al., "Absence of Lipopolysaccharide In The Lyme Disease Spirochete, \*\*\*Borrelia\*\*\* burgdorferi," Infect. Immun., 55:2311-2313 (1987). OspA and OspB lipoproteins are analogous to the VMP proteins of *B. hermsii*, and appear. . . Schoberg, R. J., et al., "Identification Of A Highly Cross-reactive Outer Surface Protein B Epitope Among Diverse Geographic Isolates of \*\*\*Borrelia\*\*\* Spp. Causing Lyme Disease," Infect Immun., 32:489-500 (1994). It appears to be responsible for the ability of *B. burgdorferi* to become resistant to the bactericidal effects of anti-OspA/OspB antibodies. Sadziene, A., et al., "Antibody-resistant Mutants of \*\*\*Borrelia\*\*\* burgdorferi: In Vitro Selection And Characterization," J. Exp. Med., 176:799-809 (1992); Coleman, J. L., et al, "Selection Of An Escape Variant Of \*\*\*Borrelia\*\*\* burgdorferi By Use Of Bactericidal Monoclonal Antibodies To OspB," Infect. Immun., 60:3098-3104 (1992). Antibodies against OspA prevent development of carditis. . . in the scid mouse. Schaible, U. E., et al., "Monoclonal Antibodies Specific For The Outer Membrane Protein A (OspA) Of \*\*\*Borrelia\*\*\* burgdorferi Prevent Lyme Disease \*\*\*Borreliosis\*\*\* In Severe Combined Immunodeficiency (Scid) Mice," Proc. Natl. Acad. Sci. USA, 87:3768-3772 (1990). The immunogenicity of OspA appears to be influenced by its lipidic content (Erdile, L. F., et al., "Role Of Attached Lipid In Immunogenicity Of \*\*\*Borrelia\*\*\* burgdorferi OspA," Infect. Immun., 61:81-90 (1993)), and, as mentioned above, the protein has been used successfully as a vaccine in. . .

SUMM . . . commensal spirochetes and with antigens of Gram-negative bacteria. Rasiah, C., et al., "Purification And Characterization Of A Tryptic Peptide Of \*\*\*Borrelia\*\*\* burgdorferi Flagellin, Which

Reduces Cross-reactivity In Immunobolots And ELISA," J. Gen. Microbiol., 138:147-154 (1992); Coleman, J. L., et al., "Characterization Of Antigenic Determinants Of \*\*\*Borrelia\*\*\* burgdorferi Shared By Other Bacteria," J. Infect. Dis., 165:658-656 (1992). B. burgdorferi flagellin has 60-95% amino acid sequence similarity to flagellins from related bacteria (Rasiah. C., et al., "Purification And Characterization Of A Tryptic Peptide Of \*\*\*Borrelia\*\*\* burgdorferi Flagellin, Which Reduces Cross-reactivity In Immunobolots And ELISA," J. Gen. Microbiol., 138:147-154 (1992); Coleman, J. L., et al., "Characterization Of Antigenic Determinants Of \*\*\*Borrelia\*\*\* burgdorferi Shared By Other Bacteria," J. Infect. Dis., 165:658-656 (1992)), 50% to unrelated ones (Rasiah. C., et al., "Purification And Characterization Of A Tryptic Peptide of \*\*\*Borrelia\*\*\* burgdorferi Flagellin, Which Reduces Cross-reactivity In Immunobolots And ELISA," J. Gen. Microbiol., 138:147-154 (1992); Coleman, J. L., et al., "Characterization Of Antigenic Determinants Of \*\*\*Borrelia\*\*\* burgdorferi Shared By Other Bacteria," J. Infect. Dis., 165:658-656 (1992)), and cross-reacts with human tissue antigens as well (Rasiah. C., et al., "Purification And Characterization Of A Tryptic Peptide Of \*\*\*Borrelia\*\*\* burgdorferi Flagellin, Which Reduces Cross-reactivity In Immunobolots And ELISA," J. Gen. Microbiol., 138:147-154 (1992); Magnarelli, L. A., et al., "Comparison Of Whole-cell Antibodies And An Antigenic Flagellar Epitope Of \*\*\*Borrelia\*\*\* burgdorferi In Serologic Tests For Diagnosis Of Lyme \*\*\*Borreliosis\*\*\* , J. Clin. Microbiol., 30:3158-3162 (1992)). In general, there is a broad cross-reactivity of B. burgdorferi proteins with proteins of other bacterial species including \*\*\*Borrelia\*\*\*, Treponema, and gram-negative rods that are capable of inducing anamnestic responses. Coleman, J. L., et al., "Characterization Of Antigenic Determinants Of \*\*\*Borrelia\*\*\* burgdorferi Shared By Other Bacteria," J. Infect. Dis., 165:658-656 (1992). Moreover, the surface of B. burgdorferi may be similar to. . .

SUMM . . . Bergstrom, S., et al., "Molecular Analysis Of Linear Plasmid-encoded Major Surface Proteins, OspA and OspB, Of The Lyme Disease Spirochete \*\*\*Borrelia\*\*\* burgdorferi," Molec. Microbiol., 3:479-486 (1989). The genetic material of B. burgdorferi consists of double-stranded linear chromosomal DNA with a putative. . .  
Bergstrom, S., et al., "Molecular Analysis Of Linear Plasmid-encoded Major Surface Proteins, OspA and OspB, Of The Lyme Disease Spirochete \*\*\*Borrelia\*\*\* burgdorferi," Molec. Microbiol., 3:479-486 (1989);  
Casjens, S., et al., "Linear Chromosomal Physical And Genetic Map Of \*\*\*Borrelia\*\*\* burgdorferi, The Lyme Disease Agent," Molec. Microbiol., 8:967-980 (1993). A 49.0 kb linear plasmid encodes the expression of the immunogenic,. . . Bergstrom, S., et al., "Molecular Analysis Of Linear Plasmid-encoded Major Surface Proteins, OspA and OspB, Of The Lyme Disease Spirochete \*\*\*Borrelia\*\*\* burgdorferi," Molec. Microbiol., 3:479-486 (1989); Coleman, J. L., et al, "Selection Of An Escape Variant Of \*\*\*Borrelia\*\*\* burgdorferi By Use Of Bactericidal Monoclonal Antibodies To OspB," Infect. Immun., 60:3098-3104 (1992). Their function in bacterial physiology and role. . .  
Bergstrom, S., et al., "Molecular Analysis Of Linear Plasmid-encoded Major Surface Proteins, OspA and OspB, Of The Lyme Disease Spirochete \*\*\*Borrelia\*\*\* burgdorferi," Molec. Microbiol., 3:479-486 (1989);  
Volkman, D. J., et al., "Characterization Of An Immunoreactive 93-kDa Core Protein Of \*\*\*Borrelia\*\*\* burgdorferi With A Human IgG Monoclonal Antibody," J. Immunol., 146:3177-3182 (1991). Molecular

genetic techniques have permitted cloning, expression, and sequencing. . . Bergstrom, S., et al., "Molecular Analysis Of Linear Plasmid-encoded Major Surface Proteins, OspA and OspB, Of The Lyme Disease Spirochete \*\*\**Borrelia*\*\*\* *burgdorferi*," Molec. Microbiol., 3:479-486 (1989); Fuchs, R., et al., "Molecular Analysis And Expression Of A \*\*\**Borrelia*\*\*\* *burgdorferi* Gene Encoding A 22 kDa Protein (pC) in *Escherichia coli*," Molec. Microbiol., 6:503-509 (1992); Lam, T. T., et al., "Outer Surface Proteins E and F of \*\*\**Borrelia*\*\*\* *burgdorferi*, The Agent Of Lyme Disease," Infect. Immun., 62:290-298 (1994). This has opened the way for chemical and structural characterization. . . Bergstrom, S., et al., "Molecular Analysis Of Linear Plasmid-encoded Major Surface Proteins, OspA and OspB, Of The Lyme Disease Spirochete \*\*\**Borrelia*\*\*\* *burgdorferi*," Molec. Microbiol., 3:479-486 (1989); Fuchs, R., et al., "Molecular Analysis And Expression Of A \*\*\**Borrelia*\*\*\* *burgdorferi* Gene Encoding A 22 kDa Protein (pC) in *Escherichia coli*," Molec. Microbiol., 6:503-509 (1992); Lam, T. T., et al., "Outer Surface Proteins E and F of \*\*\**Borrelia*\*\*\* *burgdorferi*, The Agent Of Lyme Disease," Infect. Immun., 62:290-298 (1994)); Volkman, D. J., et al., "Characterization Of An Immunoreactive 93-kDa Core Protein Of \*\*\**Borrelia*\*\*\* *burgdorferi* With A Human IgG Monoclonal Antibody," J. Immunol., 146:3177-3182 (1991); Wilske, B., et al., "Immunological And Molecular Polymorphisms Of OspC, An Immunodominant Major Outer Surface Protein Of \*\*\**Borrelia*\*\*\* *burgdorferi*," Infect. Immun., 61:2182-2191 (1993); Hansen, K., et al., "Immunochemical Characterization And Isolation Of The Gene For A \*\*\**Borrelia*\*\*\* *burgdorferi* Immunodominant 60-Kilodalton Antigen Common To A Wide Range Of Bacteria," Infect. Immun., 56:2047-2053 (1986).

Little is known, however, about . . .

SUMM . . . flagella, and cytoplasmic antigens such as heat-shock proteins. Rasiah, C., et al., "Purification And Characterization Of A Tryptic Peptide Of \*\*\**Borrelia*\*\*\* *burgdorferi* Flagellin, Which Reduces Cross-reactivity In Immunoblots And ELISA," J. Gen. Microbiol., 138:147-154 (1992); Hansen, K., et al., "Immunochemical Characterization And Isolation Of The Gene For A \*\*\**Borrelia*\*\*\* *burgdorferi* Immunodominant 60-Kilodalton Antigen Common To A Wide Range Of Bacteria," Infect. Immun., 56:2047-2053 (1986). Such responses have been detected. . . ELISA, IFA, immunoblotting, and T cell mitogenesis. Krause, A., et al., "Cellular Immune Reactivity To Recombinant OspA And Flagellin From \*\*\**Borrelia*\*\*\* *Burgdorferi* In Patients With Lyme \*\*\**Borreliosis*\*\*\* , J. Clin. Invest., 90:1077-1084 (1992); Fikrig, E., et al., "Serologic Diagnosis Of Lyme Disease Using Recombinant Outer Surface Proteins A. . . From Rats Injected With The Lyme Disease Spirochete," J. Infect. Dis., 163:656-659; Sadziene, A., et al., "In Vitro Inhibition of \*\*\**Borrelia*\*\*\* *burgdorferi* Growth By Antibodies," J. Infect. Dis., 167:165-172 (1993); Fikrig, E., et al., "Long-Term Protection Of Mice From Lyme Disease. . . *burgdorferi* antigens with host antigens may induce host tolerance and host autoimmunity. Fikrig, E., et al., "Serologic Response To The \*\*\**Borrelia*\*\*\* *Burgdorferi* Flagellin Demonstrates An Epitope Common To A Neuroblastoma Cell Line," Proc. Natl. Acad. Sci. USA, 90:183-187 (1993). The small. . . bacteria in macrophages or other immunologically hidden sites may exacerbate this situation (Montgomery, R. R., et al., "The Fate Of \*\*\**Borrelia*\*\*\* *burgdorferi*, The Agent For Lyme Disease, In Mouse Macrophages," J. Immunol., 150:909-915 (1993)). Furthermore, some patients show dissociation between humoral.

. . . B. burgdorferi antigens (Lahesmas, R., et al., "Preferential Use Of T Cell Antigen Receptor V Region Gene Segment Vbeta5.1 By \*\*\*Borrelia\*\*\* Burgdorferi Antigen-reactive T Cell Clones Isolated From A Patient With Lyme Disease," J. Immunol., 150:4125-4135 (1993)).

SUMM . . . W. T., et al., "The Major Histocompatibility Complex-restricted Response Of Recombinant Inbred Strains Of Mice To Natural Tick Transmission Of \*\*\*Borrelia\*\*\* burgdorferi," J. Exp. Med., 177:9-17 (1993). In mice, disease-susceptible (C3H) and disease-resistant (BALB/c) inbred strains have been found (De Souza, M. S., et al., "Long-Term Study Of Cell-Mediated Responses to \*\*\*Borrelia\*\*\* burgdorferi In The Laboratory Mouse," Infect. Immun., 61:1884-1822 (1993)), and patterns of antibody response to B. burgdorferi antigens are MHC-restricted. . . W. T., et al., "The Major Histocompatibility Complex-restricted Response Of Recombinant Inbred Strains Of Mice To Natural Tick Transmission of \*\*\*Borrelia\*\*\* burgdorferi," J. Exp. Med., 177:9:17 (1993)).

SUMM . . . of similar molecular weight (Karlsson, M, et al., "Comparison Of Western Blot And Enzyme-linked Immunosorbent Assay For Diagnosis Of Lyme \*\*\*Borreliosis\*\*\* , " Eur. J. Clin. Microbiol. Infect. Dis., 8:871-877 (1989); Aron-Hott, L., et al., "Lipopolysaccharide-independent Radioimmunoprecipitation And Identification Of Structural And in. . . SDS-polyacrylamide gel electrophoresis (SDS-PAGE) (Karlsson, M., et al., "Comparison Of Western Blot And Enzyme-linked Immunosorbent Assay For Diagnosis Of Lyme \*\*\*Borreliosis\*\*\* , " Eur. J. Clin. Microbiol. Infect. Dis., 8:871-877 (1989); Aron-Hott, L., et al., "Lipopolysaccharide-independent Radioimmunoprecipitation And Identification Of Structural And in. . . concentration in the sample (Karlsson, M., et al., "Comparison Of Western Blot And Enzyme-linked Immunosorbent Assay For Diagnosis Of Lyme \*\*\*Borreliosis\*\*\* , " Eur. J. Clin. Microbiol. Infect. Dis., 8:871-877 (1989); Aron-Hott, L., et al., "Lipopolysaccharide-independent Radioimmunoprecipitation And Identification Of Structural And in. . . the interpretation of immunoblots. Karlsson, M, et al., "Comparison Of Western Blot And Enzyme-linked Immunosorbent Assay For Diagnosis Of Lyme \*\*\*Borreliosis\*\*\* , " Eur. J. Clin. Microbiol. Infect. Dis., 8:871-877 (1989); Aron-Hott, L., et al., "Lipopolysaccharide-independent Radioimmunoprecipitation And Identification Of Structural And in. . .

SUMM . . . From Lyme Disease By Vaccination With OspA," Infect. Immun., 60:773-777 (1992); Fikrig, et al., "OspA Vaccination Of Mice With Established \*\*\*Borrelia\*\*\* burgdorferi Infection Alters Disease But Not Infection," Infect. Immun., 61:2553-2557 (1993). Adoptive transfer of T cells from chronically-infected C3H mice. . . infection and disease development in recipient C3H mice. De Souza, M. S., et al., "Long-Term Study Of Cell-Mediated Responses to \*\*\*Borrelia\*\*\* burgdorferi In The Laboratory Mouse," Infect. Immun., 61:1884-1822 (1993). These observations are consistent with induced protection being primarily mediated by antibodies against \*\*\*borrelial\*\*\* antigens, and not by T cell-mediated cellular immune responses. Fikrig, E., et al., "Protection Of Mice Against The Lyme Disease. . . protein provides active protection. Schaible, U. E., et al., "Monoclonal Antibodies Specific For The Outer Membrane Protein A (OspA) Of \*\*\*Borrelia\*\*\* burgdorferi Prevent Lyme Disease \*\*\*Borreliosis\*\*\* In Severe Combined Immunodeficiency (Scid) Mice," Proc. Natl. Acad. Sci. USA, 87:3768-3772 (1990); Fikrig, E., et al., "Long-Term Protection Of . . . From Lyme Disease By Vaccination With OspA," Infect. Immun.,

60:773-777 (1992); Fikrig, et al., "OspA Vaccination Of Mice With Established \*\*\*Borrelia\*\*\* burgdorferi Infection Alters Disease But Not Infection," Infect. Immun., 61:2553-2557 (1993). In scid mice, however, passive protection appears to be. . . complete only for infection by *B. burgdorferi* expressing identical or very similar OspA. Schaible, U. E., "Immune Sera To Individual \*\*\*Borrelia\*\*\* burgdorferi Isolates Or Recombinant OspA Thereof Protect SCID Mice Against Infection with Homologous Strains But Only Partially Or Not At. . . mice vaccinated with OspB. Bockenstedt, L. K., et al., "Inability Of Truncated Recombinant OspA Proteins To Elicit Protective Immunity To \*\*\*Borrelia\*\*\* burgdorferi In Mice," J. Immunol., 151:900-906 (1993); Fikrig, E., et al., "Evasion Of Protective Immunity By \*\*\*Borrelia\*\*\* burgdorferi By Truncation Of Outer Surface Protein B.," Proc. Nat. Acad. Sci. USA, 90:4092-4096 (1993). *B. burgdorferi* variants lacking expression. . . even against challenges with strains expressing OspA/OspB antigens. Norton Hughes, C. A., et al., "Protective Immunity Is Induced By A \*\*\*Borrelia\*\*\* burgdorferi Mutant That Lacks OspA and OspB," Infect. Immun., 61:5151-5122 (1993). These experiments suggest that plasmid-encoded OspA/OspB are not the. . . only *B. burgdorferi* antigens that can confer protection. Norton Hughes, C. A., et al., "Protective Immunity Is Induced By A \*\*\*Borrelia\*\*\* burgdorferi Mutant That Lacks OspA and OspB," Immun., 61:5151-5122 (1993). Another property of plasmids that makes plasmid-encoded gene products less. . . And Microevolution Of The Antibiotic Resistance Plasmids R6-5," Mol. Gen. Genet., 167:11-19 (1978); Schaible, U. E., "Immune Sera To Individual \*\*\*Borrelia\*\*\* burgdorferi Isolates Or Recombinant OspA Thereof Protect SCID Mice Against Infection with Homologous Strains But Only Partially Or Not At. . . Genotype," Vaccine, 11:1049-1054 (1993); Bockenstedt, L. K., et al., "Inability Of Truncated Recombinant OspA Proteins To Elicit Protective Immunity To \*\*\*Borrelia\*\*\* burgdorferi In Mice," J. Immunol., 151:900-906 (1993); Norton Hughes, C. A., et al., "Protective Immunity Is Induced By A \*\*\*Borrelia\*\*\* burgdorferi Mutant That Lacks OspA and OspB," Infect. Immun., 61:5151-5122 (1993).

SUMM The present invention relates to an isolated membrane protein or polypeptide encoded by chromosomal DNA of \*\*\*Borrelia\*\*\* burgdorferi. The isolated protein or polypeptide of the present invention can be combined with a pharmaceutically-acceptable carrier to form a vaccine or used alone for administration to mammals, particularly humans, in preventing infection by \*\*\*Borrelia\*\*\* burgdorferi. Alternatively, the protein or polypeptide of the present invention can be used to raise an antibody or a binding. . . portions thereof may be used alone or combined with a pharmaceutically-acceptable carrier to treat mammals, particularly humans, already exposed to \*\*\*Borrelia\*\*\* burgdorferi, to induce a passive immunity to prevent disease occurrence.

SUMM . . . invention or the antibodies or binding portions thereof raised against them can be utilized in a method for detection of

\*\*\*Borrelia\*\*\* burgdorferi or responses induced in infected hosts in a sample of tissue or body fluids. When the protein or polypeptide. . . antigen. Any reaction with the antigen or the antibody is detected using an assay system which indicates the presence of \*\*\*Borrelia\*\*\* burgdorferi or host immune response to it in the sample. Alternatively,

\*\*\*Borrelia\*\*\* burgdorferi can be detected in such a sample by providing a nucleotide sequence of the gene encoding protein or polypeptide. . . procedure (e.g., using a polymerase chain reaction

procedure). Any reaction with the probe is detected so that the presence of \*\*\*Borrelia\*\*\* burgdorferi in the sample is indicated.

SUMM Isolation of the protein or polypeptide of the present invention constitutes a significant advance in the treatment and detection of

\*\*\*Borrelia\*\*\* burgdorferi. Since it is a chromosomally-encoded gene product of \*\*\*Borrelia\*\*\* burgdorferi, it provides a more genetically stable immunogen for a Lyme disease vaccine than plasmid-encoded gene products. Moreover, such proteins. . .

DRWD . . . shows the deduced amino acid sequence (SEQ. ID No. 1) and complete nucleotide sequence (SEQ. ID. No. 2) of the \*\*\*Borrelia\*\*\* burgdorferi BmpC proteins and bmpC gene, respectively. Potential promoters are indicated by a double underline. A ribosome binding site (positions. . .

DRWD . . . nylon membrane, and probed with bmpC-specific fragment. Lane 1: strain 297 (B. burgdorferi sensu stricto); Lane 2: strain 20047 (B. \*\*\*garinii\*\*\* ); Lane 3: strain \*\*\*IP90\*\*\* (B. \*\*\*garinii\*\*\* ); Lane 4: strain IP3 (B. afzelii).

DETD The present invention relates to an isolated membrane protein or polypeptide encoded by chromosomal DNA of \*\*\*Borrelia\*\*\* burgdorferi. This isolated protein, BmpC, has a calculated isoelectric point of about 9.6. BmpC also has about a 35-45% homology. . . and BmpB protein or polypeptide identified in W. J. Simpson, et al., "Nucleotide Sequence and Analysis of the Gene in \*\*\*Borrelia\*\*\* burgdorferi Encoding Immunogenic P39 Antigen," FEMS Letters, 119:381-88 (1994), which is hereby incorporated by reference. The BmpC protein or polypeptide. . . invention has one or more antigenic determinants conferring on the protein the ability to recognize antisera for mammals infected with \*\*\*Borrelia\*\*\* burgdorferi. The BmpC protein or polypeptide has an amino acid sequence corresponding to SEQ. ID. No. 1 as follows:

DETD In \*\*\*Borrelia\*\*\* burgdorferi, the protein or polypeptide of the present invention is believed to be present as a membrane lipoprotein.

DETD In \*\*\*Borrelia\*\*\* burgdorferi, the BmpC DNA molecule is part of a gene located at about 400 kbp on a chromosomal map of \*\*\*Borrelia\*\*\* burgdorferi. It is immediately upstream of the genes encoding for the proteins BmpA and BmpB (i.e. bmpA and bmpB, respectively).

DETD . . . BmpC protein or polypeptide, a wide array of therapeutic and/or prophylactic agents and diagnostic procedures for, respectively, treating and detecting \*\*\*Borrelia\*\*\* burgdorferi can be developed.

DETD . . . administered alone or in combination with a pharmaceutically-acceptable carrier to mammals, particularly humans, as a vaccine, for preventing infection by \*\*\*Borrelia\*\*\* burgdorferi. Alternatively, it is possible to administer to individuals exposed to \*\*\*Borrelia\*\*\* burgdorferi with an effective amount of an antibody or binding portion thereof against that protein or polypeptide as a passive. . . in combination with a pharmaceutically-acceptable carrier to effect short term treatment of individuals who may have been recently exposed to \*\*\*Borrelia\*\*\* burgdorferi.

DETD . . . present invention can be used as antigens in diagnostic assays for the detection of immune cells or antibodies reactive against \*\*\*Borrelia\*\*\* burgdorferi in body fluids. Alternatively, the detection of that organism can be achieved with a diagnostic assay employing antibodies or binding portions thereof raised by such antigens. Such techniques permit detection of \*\*\*Borrelia\*\*\* burgdorferi in a sample of the following tissue or body fluids: blood,

spinal fluid, sputum, pleural fluids, urine, bronchial alveolar. . .

DETD . . . molecule of the present invention may be used as a probe in nucleic acid hybridization assays for the detection of \*\*\*Borrelia\*\*\* burgdorferi in various patient body fluids. The nucleotide sequence of the present invention may be used in any nucleic acid. . .

DETD . . . DNA sequencing were performed, as described in Schwartz, J. J., et al., "RNA Gene Organization in the Lyme Disease Spirochete, \*\*\*Borrelia\*\*\* burgdorferi," J. Bacteriol. 174:3757-3765 (1992), which is hereby incorporated by reference. The double-stranded dideoxy method with modified T7 DNA polymerase. . . hybridization was performed essentially as described in Schwartz, J. J., et al., "RNA Gene Organization in the Lyme Disease Spirochete, \*\*\*Borrelia\*\*\* burgdorferi," J. Bacteriol. 174:3757-3765 (1992), which is hereby incorporated by reference, except that the probes were labelled with digoxigenin, and. . .

DETD DNA Sequence Analysis of \*\*\*Borrelia\*\*\* burgdorferi bmpC

DETD . . . end of B. burgdorferi 16S RNA (Gazumyan, A., "Sequence Analysis of the Ribosomal RNA Operon of the Lyme Disease Spirochete, \*\*\*Borrelia\*\*\* burgdorferi," Gene, 146:57-65 (1994), which is hereby incorporated by reference) and is initiated with a TTG codon. The use of. . .

DETD . . . of the recently described bmpA and bmpB (Simpson, W. J., et al., "Nucleotide Sequence and Analysis of the Gene in \*\*\*Borrelia\*\*\* burgdorferi Encoding Immunogenic P39 Antigen," FEMS Microbiol. Letters 119:381-388 (1994), which is hereby incorporated by reference) at approximately 400 Kbp on the linear B. burgdorferi chromosome map.

Casjens, S., et al., "Linear Chromosomal Physical and Genetic Map of \*\*\*Borrelia\*\*\* burgdorferi, the Lyme Disease Agent," Mol. Microbiol. 8:967-980 (1993), which is hereby incorporated by reference. bmpC is separated from the. . . ATG at nucleotide 1281 in FIG. 1. Simpson, W. J., et al., "Nucleotide Sequence and Analysis of the Gene in \*\*\*Borrelia\*\*\* burgdorferi Encoding Immunogenic P39 Antigen," FEMS Microbiol. Letters 119:381-388 (1994), which is hereby incorporated by reference. The location of these. . . putative promoter sequences occur upstream of bmpC. Simpson, W. J., et al., "Nucleotide Sequence and Analysis of the Gene in \*\*\*Borrelia\*\*\* burgdorferi Encoding Immunogenic P39 antigen," FEMS Microbiol. Letters 119:381-388 (1994), which is hereby incorporated by reference, suggested the existence of. . . promoter-like sequences were found upstream of bmpB. Simpson, W. J., et al., "Nucleotide Sequence and Analysis of the Gene in \*\*\*Borrelia\*\*\* burgdorferi Encoding Immunogenic P39 Antigen," FEMS Microbiol. Letters 119:381-388 (1994), which is hereby incorporated by reference. These observations strengthen the. . .

DETD . . . with those of BmpA and BmpB, respectively. Simpson, W. J., et al., "Nucleotide Sequence and Analysis of the Gene in \*\*\*Borrelia\*\*\* burgdorferi Encoding Immunogenic P39 Antigen," FEMS Microbiol. Letters 119:381-388 (1994). The three sequences show 26% sequence identity (i.e., identical amino. . .

DETD . . . BmpB with TmpC (27% and 32%, respectively). Simpson, W. J., et al., "Nucleotide Sequence and Analysis of the Gene in \*\*\*Borrelia\*\*\* burgdorferi Encoding Immunogenic P39 Antigen," FEMS Microbiol. Letters, 119:381-88 (1994), which is hereby incorporated by reference. All these proteins have. . . peptidase II sites, suggesting that they are lipoproteins and are probably located in either the cytoplasmic or outer membrane of \*\*\*Borrelia\*\*\* burgdorferi.

DETD . . . if bmpC was present in all *B. burgdorferi* strains. Chromosomal DNA from representative *B. burgdorferi* sensu stricto (strain 297), *B. garinii* (strains 20047 and IP90) and *B. afzelii* (strain IP3) were digested with HincII and the resultant blot was developed with a bmpC probe (FIG. . .).

DETD The Bmp proteins described here and by Simpson, W. J., et al., "Nucleotide Sequence and Analysis of the Gene in \*\*\**Borrelia*\*\*\* *burgdorferi* Encoding Immunogenic P39 Antigen," FEMS Microbiol. Letters 119:381-388 (1994), which is hereby incorporated by reference, are the first examples. . . plasmid encoded. Howe, T. R., et al, "Organization of Genes Encoding Two Outer Membrane Proteins of the Lyme Disease Agent \*\*\**Borrelia*\*\*\* *burgdorferi* Within a Single Transcriptional Unit," Infect. Immun. 54:207-212 (1986); Marconi, R. T., et al., "Transcriptional Analysis and Mapping of. . .

CLM What is claimed is:

. . . wherein said protein or polypeptide is encoded by a gene located at about 400 kbp on a chromosomal map of \*\*\**Borrelia*\*\*\* *burgdorferi*.

L15 ANSWER 8 OF 21 USPATFULL

AN 2001:93284 USPATFULL

TI Decorin binding protein compositions and methods of use

IN Guo, Betty P., Boston, MA, United States

Hook, Magnus, Houston, TX, United States

PA The Texas A & M University System, College Station, TX, United States  
(U.S. corporation)

PI US 6248517 B1 20010619

WO 9634106 19961031

AI US 1997-945476 19971224 (8)

WO 1996-US5886 19960424

19971224 PCT 371 date

19971224 PCT 102(e) date

RLI Continuation-in-part of Ser. No. US 1996-589711, filed on 22 Jan 1996,  
now patented, Pat. No. US 5853987 Continuation-in-part of Ser. No. US  
1995-427023, filed on 24 Apr 1995, now abandoned

DT Utility

FS GRANTED

EXNAM Primary Examiner: Zitomer, Stephanie W..

LREP Williams, Morgan and Amerson

CLMN Number of Claims: 57

ECL Exemplary Claim: 1

DRWN 42 Drawing Figure(s); 28 Drawing Page(s)

LN.CNT 4945

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\**Borrelia*\*\*\* *burgdorferi*, the etiological agent of Lyme disease, and DNA segments encoding dbp from related \*\*\**borrelia*\*\*\*. Also disclosed are decorin binding protein compositions and methods of use. The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathological \*\*\**Borrelia*\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and anti-(decorin binding protein) antibodies will also be of use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\**Borrelia*\*\*\*

colonization in an animal. These DNA segments and the peptides derived therefrom are contemplated for use in the preparation of vaccines and, also, for use as carrier proteins in vaccine formulations, and in the formulation of compositions for use in the prevention of Lyme disease.

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\*Borrelia\*\*\* burgdorferi, the etiological agent of Lyme disease, and DNA segments encoding dbp from related \*\*\*borrelia\*\*\*. Also disclosed are decorin binding protein compositions and methods of use. The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathological \*\*\*Borrelia\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and . . . of use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\*Borrelia\*\*\* colonization in an animal. These DNA segments and the peptides derived therefrom are contemplated for use in the preparation of. . .

SUMM . . . proteins derived from bacterial species. More particularly, the invention provides gene compositions encoding a decorin (Dcn) binding protein (DBP) from \*\*\*Borrelia\*\*\* burgdorferi and the corresponding peptide epitopes and protein sequences comprising native and synthetically-modified Dcn binding site domains. Various methods for. . .

SUMM Lyme disease (Steere, 1989), or Lyme \*\*\*borreliosis\*\*\*, is transmitted by ticks, particularly of the genus Ixodes, and caused by spirochetes of the genus \*\*\*Borrelia\*\*\*. Lyme disease agents, that is \*\*\*borrelia\*\*\* isolated from humans or animals with clinical Lyme disease, are currently classified into at least three phylogenetic groups: B. burgdorferi sensu stricto, B. \*\*\*garinii\*\*\*, and B. afzelii. Strains potentially representing other phylogenetic groups of Lyme disease agents as well, such as group 25015, have. . .

SUMM . . . vitro-grown or tick-borne B. burgdorferi. Based largely on the protective efficacy of experimental OspA vaccines in rodent models of Lyme \*\*\*borreliosis\*\*\*, three monovalent OspA-based vaccines are currently in clinical trials. However, recent findings suggest that broad, sustained protection of humans may. . .

SUMM c) OspA is serologically diverse, particularly among European and Asian B. \*\*\*garinii\*\*\* and B. afzelii isolates. Reactivity with panels of OspA monoclonal antibodies (mAbs), and DNA sequence analysis has shown that as. . .

SUMM . . . and Bockenstedt, 1993). OspA is expressed by B. burgdorferi within ticks (Barbour et al., 1983), but detection of OspA on \*\*\*borrelia\*\*\* in tissue early after infection is difficult. Passive immunization of mice with OspA antibody (Schaible et al., 1990), or immunization. . .

SUMM . . . vivo only at later stages when the infection becomes disseminated. This would be explained by down-regulation of OspA expression by \*\*\*borrelia\*\*\* shortly after initiation of feeding by the tick.

SUMM . . . it has been demonstrated that when OspA-specific antibodies were administered to mice before or at the time of attachment of \*\*\*borrelia\*\*\*-infected ticks these mice were protected from spirochetal infection. However, when OspA-specific antibody was administered 48 hr after tick attachment no. . .

SUMM Modulation of \*\*\*borrelia\*\*\* antigen expression within feeding ticks

has recently been reported for OspC; initially low in resting ticks, OspC levels increase on. . .

SUMM . . . to pre-exist at high levels in human or animal hosts prior to the tick bite to be effective against OspA-expressing \*\*\*borrelia\*\*\* in the tick, and may receive little or no boosting upon delivery of the spirochetes into the skin within the. . .

SUMM . . . the gut of the infecting tick, before inoculation of the pathogen." Consistent with this hypothesis it has been shown that anti- \*\*\*borrelia\*\*\* serum can protect mice from infection by tick bite if administered within two days after initiation of feeding by \*\*\*borrelia\*\*\* -infected ticks, but not when passively administered at later times (Shih et al., 1995). The antibody levels in response to recombinant. . .

SUMM . . . the host cell ECM component, Dcn. Also disclosed are methods for active and passive immunization against *B. burgdorferi* and related \*\*\*borrelia\*\*\* including *B. afzelii* and *B. \*\*\*garinii\*\*\** using novel native and site-specifically-altered DBP compositions and DBP-derived epitopic peptides from *B. burgdorferi*, *B. afzelii* and *B. \*\*\*garinii\*\*\**. Particular aspects of the invention relate to novel nucleic acid segments encoding these peptides and epitopes, and methods for the. . .

SUMM . . . OspA as antibodies reactive with DBP derived from *B. burgdorferi* sensu stricto are also growth-inhibitory to many strains of *B. \*\*\*garinii\*\*\** and *B. afzelii*;

SUMM (3) Antiserum against DBP.sub.297 provides either complete or partial protection against several additional heterologous *B. burgdorferi*, *B. afzelii*, and *B. \*\*\*garinii\*\*\** strains;

SUMM . . . and isolate molecular clones of alleles of this gene present in different phylogenetic groups of Lyme disease spirochetes including *B. \*\*\*garinii\*\*\**, *B. japonica*, *B. afzelii*, and related \*\*\*Borrelia\*\*\* spp. by utilization of PCR.TM. techniques. These new dbp alleles have been shown to have a high level of sequence. . .

SUMM . . . SEQ ID NO:22, SEQ ID NO:24, or SEQ ID NO:26 encoding the DBP of strains 297, B31, Sh.2.82, HB-19, PGau, \*\*\*IP90\*\*\*, LP4, LP7, and JD1, respectively. One of skill in the art will understand that strain variants of DBP include those. . .

SUMM SEQ ID NO:7 comprises the complete nucleotide sequence of a 2.5-kb insert of \*\*\*borrelia\*\*\* genomic DNA cloned in the pBlueScript.TM. vector. This recombinant clone, designated BG26:pB/2.5(5), has been deposited with the American Type Culture. . .

SUMM . . . DBPs. Strain variants are those nucleic acid compositions and polypeptide compositions expressed by various strains of *B. burgdorferi* and related \*\*\*borrelia\*\*\* including *B. afzelii* and *B. \*\*\*garinii\*\*\** which specifically encode DBPs. These DBPs also bind Dcn and related proteoglycans and share similarity of structure and function with. . . *burgdorferi* strain 297 encoded by the nucleic acid sequences of SEQ ID NO:7 and SEQ ID NO:8, and the related \*\*\*borrelia\*\*\* DBPs of strains B31, Sh.2.82, HB-19, LP4, LP7, and JD1 of *B. burgdorferi* (SEQ ID NO:12, SEQ ID NO: 14, . . . ID NO:22, SEQ ID NO:24, and SEQ ID NO:26, respectively); strain pGau (SEQ ID NO:18) of *B. afzelii*; or strain \*\*\*IP90\*\*\* (SEQ ID NO:20) of *B. \*\*\*garinii\*\*\**

SUMM . . . alternatively by demonstrating the ability of the strain-variant DBP to lessen or prevent adherence of *B. burgdorferi* and related \*\*\*borrelia\*\*\* including *B. afzelii* and *B. \*\*\*garinii\*\*\**

to Dcn.

SUMM . . . NO:24), or FIG. 19 (SEQ ID NO:26) or strain variants or active fragments thereof encoding all or portions of a \*\*\*borrelial\*\*\* DBP.

SUMM . . . a DBP is also understood to mean a polypeptide that is immunologically reactive with antibodies generated against B. burgdorferi, B. \*\*\*garinii\*\*\*, B. afzelii or related \*\*\*Borrelia\*\*\* spp. and in particular antibodies generated against any of the DBPs encoded by the nucleic acid sequences of any of. . .

SUMM . . . a treated animal, this immune response being effective to lessen or prevent symptomatic disorders associated with Lyme disease or related \*\*\*borrelioses\*\*\*, or which polypeptide is also capable of eliciting antibodies that are immunologically reactive with DBP encoded by a nucleic acid. . .

SUMM . . . and peptides, in particular those DBP proteins isolated from prokaryotic sources, and particularly bacteria. DNA segments isolated from species of \*\*\*Borrelia\*\*\* and related bacteria which are shown to bind Dcn are particularly preferred for use in the methods disclosed herein. Such. . .

SUMM . . . particularly contemplated to be useful in the production of Anti-DBP antibodies for use in passive immunization methods for prevention of \*\*\*borrelial\*\*\* adhesion to Dcn, and treatment of infections due to \*\*\*Borrelia\*\*\* invasion, and particularly invasion by B. burgdorferi.

SUMM . . . be used, so long as the coding segment employed encodes a protein or peptide of interest (e.g., a DBP from \*\*\*Borrelia\*\*\*, and particularly a DBP from B. burgdorferi, B. afzelii, or B. \*\*\*garinii\*\*\*, and does not include any coding or regulatory sequences that would have an adverse effect on cells. Therefore, it will. . .

SUMM . . . that it will direct the expression and production of the protein or peptide epitope of interest (e.g., a DBP from \*\*\*Borrelia\*\*\* and in particular, from B. burgdorferi, B. afzelii, B. \*\*\*garinii\*\*\*, or B. japonica) when incorporated into a host cell. In a recombinant expression vector, the coding portion of the DNA. . .

SUMM . . . The nucleic acid sequences encoding DBP are useful as diagnostic probes to detect the presence of B. burgdorferi, and related \*\*\*borrelias\*\*\* including B. afzelii and B. \*\*\*garinii\*\*\* in a test sample, using conventional techniques. In one such method of diagnosing \*\*\*Borrelial\*\*\* infection, dbp nucleic acid segments may be used in Southern hybridization analyses or Northern hybridization analyses to detect the presence. . .

SUMM . . . antibodies for diagnostic and therapeutic methods relating to the detection and treatment of infections caused by B. burgdorferi and related \*\*\*borrelias\*\*\* including B. afzelii and B. \*\*\*garinii\*\*\*

SUMM . . . serum concentration of DBP-reactive antibodies that is at least twice that required for inhibition of in vitro growth of endemic \*\*\*borrelia\*\*\* strains. It is contemplated that the duration of dosing maintaining anti-DBP levels at these inhibitory antibody concentrations would be for. . .

SUMM . . . length will often be preferred. The antigenic proteins or peptides may also be combined with other agents, such as other \*\*\*borrelial\*\*\* peptide or nucleic acid compositions, if desired.

SUMM . . . methods for the stimulation of an immune response include vaccination regimens designed to prevent or lessen significant infections caused by \*\*\*borrelias\*\*\* or other bacteria expressing a

DBP, and treatment regimens that may lessen the severity or duration of any infection, it . . . treatment methods may be used particularly for the treatment of infections caused by pathogens such as *B. burgdorferi*, *B. afzelii*, *B. \*\*\*garinii\*\*\**, related \*\*\*borrelial\*\*\* species, and other bacteria which express DBPs and adhere to Dcn.

SUMM Immunoformulations of this invention, whether intended for vaccination, treatment, or for the generation of antibodies useful in the detection of \*\*\*borrelia\*\*\* and in particular *B. burgdorferi*, the prevention of bacterial adhesion, or in the case of bacterial colonization, promotion of bacterial. . .

SUMM . . . in the immunodetection of compounds, present within clinical samples, that are indicative of Lyme disease or related infections caused by \*\*\*borrelia\*\*\*, and in particular *B. burgdorferi*. The kits may also be used in antigen or antibody purification, as appropriate.

SUMM . . . even perhaps urine samples may be employed. This allows for the diagnosis of Lyme disease and related infections caused by \*\*\*borrelia\*\*\*, and in particular, *B. burgdorferi*. Furthermore, it is contemplated that such embodiments may have application to non-clinical samples, such as. . .

SUMM . . . of a therapeutically effective dose of DBP to a subject induces in the subject antibodies which bind and neutralize a \*\*\**Borrelia*\*\*\* bacterium (and particularly *B. burgdorferi*, *B. \*\*\*garinii\*\*\**, *B. afzelii*, *B. japonica* and related \*\*\**Borrelia*\*\*\* spp.), present in the subject, thereby preventing the deleterious effects of this microorganism. Alternatively, anti- \*\*\**Borrelia*\*\*\* antibodies, and in particular, anti-*B. burgdorferi*, *B. \*\*\*garinii\*\*\**, *B. afzelii*, *B. japonica* and related \*\*\**Borrelia*\*\*\* spp. antibodies generated in a first host animal provide antibodies which can be administered to a second subject for passive immunization or treatment against *B. burgdorferi*, *B. \*\*\*garinii\*\*\**, *B. afzelii*, or *B. japonica* infection. Such anti- \*\*\**Borrelia*\*\*\* antibodies are also useful as a diagnostic screen for the presence of \*\*\**Borrelia*\*\*\*, and in particular *B. burgdorferi*, *B. \*\*\*garinii\*\*\**, *B. afzelii*, *B. japonica* or related \*\*\**Borrelia*\*\*\* spp. in a test sample, using conventional immunoassay techniques.

SUMM . . . novel DBPs of *B. burgdorferi* strains 297, B31, Sh.2.82, HB-19, LP4, LP7 and JD1; *B. afzelii* strain PGau, and *B. \*\*\*garinii\*\*\** strain \*\*\*IP90\*\*\*. Strain variants are prepared and screened by amplification of nucleic acid sequences of other stains of *B. burgdorferi* or similar. . .

SUMM . . . vaccine compositions useful in the prevention of Lyme disease and antibody compositions useful in the prevention of Dcn binding to \*\*\**Borrelia*\*\*\*.

SUMM . . . bacterial cells. These aspects provide methods and compositions for producing bacterial colonization of an animal host with attenuated, or avirulent \*\*\**Borrelia*\*\*\* expressing cell surface DBP epitopes.

SUMM . . . with an antibody composition disclosed herein, and detecting the formation of immune complexes. In preferred embodiments, the bacterium is a \*\*\**Borrelia*\*\*\*, and most preferably, a *B. burgdorferi*, *B. afzelii*, or *B. \*\*\*garinii\*\*\** strain.

SUMM . . . include pharmaceutically-acceptable formulations of either the antibodies or peptide antigens disclosed herein. Such kits are useful in the detection of \*\*\**Borrelia*\*\*\* in clinical samples, and also useful for inhibiting or promoting the binding of \*\*\**Borrelia*\*\*\* to

the ECM component, Dcn. In preferred embodiments, the bacteria detected using such kits include \*\*\*borrelia\*\*\*, and in particular, B. burgdorferi, B. afzelii, B. \*\*\*garinii\*\*\*, or related species.

SUMM Other aspects of the invention include methods of inhibiting bacterial colonization, and particularly colonization by \*\*\*borrelia\*\*\*, in an animal by administering to the animal an antibody of the present invention which prevents or significantly reduces the. . . the antibody composition may be prophylactically prior to and/or following diagnosis of Lyme disease or other multisystemic disorders caused by \*\*\*Borrelioses\*\*\* which may involve the skin, joints, heart, and central nervous system. The administration may also be made in passive immunization. . .

SUMM . . . other Gram-negative hosts including various Pseudomonas species may be used in the recombinant expression of the genetic constructs disclosed herein. \*\*\*Borrelia\*\*\* themselves may be used to express these constructs, and in particular, B. burgdorferi, B. afzelii, B. japonica and B. \*\*\*garinii\*\*\*.

DRWD FIG. 16. Nucleotide and deduced amino acid sequence of B. \*\*\*garinii\*\*\* strain \*\*\*IP90\*\*\* DNA encoding DBP (SEQ ID NO:20). The translated amino acid sequence is given in SEQ ID NO:21.

DRWD . . . at day 2. At two weeks post-challenge tissue samples (bladder, ear) were placed in BSK II medium and evidence of \*\*\*borrelial\*\*\* outgrowth from these tissues was assessed microscopically after 2 wk of in vitro culture at 34.degree. C.; 10-20 high power fields of samples of the cultures were examined before judging tissues to be uninfected. The number of visible \*\*\*borrelia\*\*\* per microscopic field in organ cultures from each mouse are shown.

DRWD FIG. 21. Membrane localization of candidate \*\*\*borrelia\*\*\* vaccine antigens. B. burgdorferi B31 total membranes were separated into inner-(IM, lane 2) and outer-membranes (OM, lane 4) using. . . by others (Bledsoe et al., 1994). By detergent phase portioning DBP appears to be amphiphilic as are OspA and other \*\*\*borrelia\*\*\* membrane lipoproteins (Brandt et al., 1990).

DRWD . . . Five combinations of these oligonucleotides were used as primer pairs for PCR.TM. amplification studies with genomic DNA templates from various \*\*\*borrelia\*\*\* strains. The sizes, in base pairs, of the dbp gene segments expected, based on the strain 297 sequence, from these. . .

DRWD FIG. 25. Comparison of amino acid sequence identities for the DBPs from related \*\*\*borrelia\*\*\*. The predicted DBP amino acid sequences disclosed herein were compared in a pairwise fashion as to % identity using the. . .

DETD . . . is anticipated to be especially effective in treatment regimens for Lyme disease, and as a cost-effective prophylaxis for prevention of \*\*\*borrelial\*\*\* infections.

DETD . . . limitations of the prior art, particularly with respect to OspA and other antigens previously investigated as antigens for development of \*\*\*borrelia\*\*\* vaccines. Indeed, vaccine compositions comprising DBPs are likely to be superior to those previously available containing OspA alone.

DETD . . . of OspA as antibodies reactive with DBP derived from B. burgdorferi sensu stricto are also growth-inhibitory to strains of B. \*\*\*garinii\*\*\* and B. afzelii.

DETD 4.2.5 Anti-DBP Antibodies Eliminate \*\*\*Borrelia\*\*\* from Infected Animals

DETD 4.2.6 dbp Nucleic Acid Segments are Useful in Identifying

\*\*\*Borrelial\*\*\* Isolates

DETD . . . and isolate molecular clones of alleles of this gene present in different phylogenetic groups of Lyme disease spirochetes including B. \*\*\*garinii\*\*\* and B. afzelii by utilization of such techniques as PCR.TM..

DETD . . . kDa. However, due to the copurification of the DBP with other B. burgdorferi proteins, complete purification of native DBP from \*\*\*borrelia\*\*\* in pure form has not been achieved.

DETD . . . antibodies to gene products encoded by such nucleic acid segments, or in the production of diagnostic and treatment protocols for \*\*\*borrelia\*\*\* infection, and in particular, infection with B. burgdorferi, B.afzelii, or B. \*\*\*garinii\*\*\* , and those infections leading to Lyme disease. Any and all such combinations are intended to fall within the scope of. . .

DETD . . . from which the DBP composition may be applied to a tissue site, skin lesion, wound area, or other site of \*\*\*borrelia\*\*\* infection. However, the single container means may contain a dry, or lyophilized, mixture of a DBP composition, which may or. . .

DETD . . . analyze the distribution of bacteria expressing DBPs during cellular infection, for example, to determine the cellular or tissue-specific distribution of \*\*\*borrelia\*\*\* under different physiological conditions. A particularly useful application of such antibodies is in purifying native or recombinant DBPs, for example,. . .

DETD 4.14 DBP Compositions for Treating \*\*\*Borrelia\*\*\* Infections

DETD . . . quantities. The selected antigens, and variants thereof, are proposed to have significant utility in diagnosing and treating infections cause by \*\*\*borrelia\*\*\* and in particular, B. burgdorferi, B. \*\*\*garinii\*\*\* and B. afzelii. For example, it is proposed that rDBPs, peptide variants thereof, and/or antibodies against such rDBPs may also be used in immunoassays to detect \*\*\*borrelia\*\*\* or as vaccines or immunotherapeutics to treat \*\*\*borrelia\*\*\* infections, and to prevent bacterial adhesion to ECM components such as Dcn in the same manner as native DBP compositions. . .

DETD . . . The peptides provided by this invention are ideal targets for use as vaccines or immunoreagents for the treatment of various \*\*\*borrelia\*\*\* -related diseases, and in particular, those caused by species which contain DBP and DBP-encoding genes, and hence those which express either. . .

DETD The \*\*\*Borrelia\*\*\* binding site on the Dcn molecule has not been identified. Presumably, Dcn binds both collagen and \*\*\*borrelia\*\*\* at once, with the two interactions involving different sites on the proteoglycan. The requirement of intact Dcn adhesin on the. . .

DETD . . . adhesive function of DBP, and its role as a target for growth-inhibitory antibodies, imply that DBP is localized to the \*\*\*borrelia\*\*\* outer membrane. To provide additional biochemical support for this B. burgdorferi B3 total membranes were separated into inner and outer. . . (Bledsoe et al., 1994). By detergent phase portioning DBP appears to be amphiphilic (FIG. 13) as are OspA and other \*\*\*borrelia\*\*\* membrane lipoproteins (Brandt et al., 1990). To confirm the presence of lipid on these proteins B. burgdorferi B31 was metabolically. . .

DETD Identification of DBPs in \*\*\*Borrelia\*\*\* Isolates

DETD One aspect of the present invention, is the identification of

\*\*\*borrelia\*\*\* using the DBP compositions disclosed herein as diagnostic indicators of \*\*\*borrelial\*\*\* infection. As shown in Table 2, an assay of DBP in \*\*\*borrelia\*\*\* using Western hybridization analyses, it was possible to identify the presence of DBPs in at least 13 strains of *B. burgdorferi*, 5 strains of *B.*

\*\*\*garinii\*\*\*, and at least three strains of *B. afzelii*. These methods represent important diagnostic tools for the identification of bacteria in. . .

DETD TABLE 2

Assay of DBP in \*\*\*Borrelia\*\*\* By Western Blot

Strain	Origin	DBP	Source
<i>B. burgdorferi</i>			
N40	tick	+	S. Norris
N40	tick	+	S. Norris
Sh2. . .	skin	+	J. Leong
G39/40	tick	+	J. Leong
297	CSF	+	R. Isaacs
25015	tick	+	M. Hanson
<i>B. garinii</i>			
PBi	CSF	+	J. Leong
PBi	CSF	+	J. Leong
G2	CSF	+	J. Leong
PBr	CSF	+	M. Hanson
B4-91	Skin	+	M. Hanson
***IP90***		tick	+
M. Hanson			
<i>B. afzelii</i>			
PKo	skin	+	M. Hanson
ACA1	skin	+	M. Hanson
PGau	skin	+	M. . .

DETD . . . the DBP DNA sequence of strain 297 were used as primers for PCR.TM. amplifications of dbp gene fragments from various

\*\*\*borrelia\*\*\* strains. Using a western blot-like assay with tagged decorin for assessment of decorin binding activity, all strains shown except HB-19. . .

DETD DBP Compositions Block Adherence of \*\*\*Borrelia\*\*\* to Decorin  
DETD Inhibitory Activity of Anti-rDBP Serum Towards In Vitro Growth of

\*\*\*Borrelia\*\*\* Strains of Diverse Origin

DETD Two other \*\*\*borrelial\*\*\* proteins, OspA and OspB, believed to be surface-exposed have been shown to be targets for bacterial killing by specific antibodies. . .

DETD Table 6 shows the growth inhibitory activity of anti-rDBP serum for diverse \*\*\*borrelia\*\*\* strains. The sensitivity of *B. burgdorferi* to growth in the presence of various antibodies in the absence of complement was. . . titration assay performed in microtiter plates.

Rabbit antisera were serially diluted in 96-well plates in 0.1 ml BSKII medium, 10.sup.5 \*\*\*borrelia\*\*\* in the mid-log phase of growth in 0.1 ml BSKII medium were added per well, the mixture was incubated for. . . sensu stricto strains tested expressing DBP (HB-19 does not express DBP in vitro), as well as several of the *B. garinii*\*\*\* and *B. afzelii* strains. One *B. afzelii* strain, PGau, was slightly inhibited at a 1:50 serum dilution. Strain 25015 was. . . into at least four OspA serogroups, and have diverse geographic origins. Serum against an irrelevant antigen, PspA, was not inhibitory.

\*\*\*Borrelia\*\*\* strains were obtained from Drs. Steve Norris, John Leong, Alan Barbour, Robert Lane, Robin Isaacs, David Dorward, and Steve

Bartold.

DETD TABLE 6

Growth Inhibitory Activity of Anti-rDB.sub.297 Serum  
Against Diverse \*\*\*Borrelia\*\*\*

Strain	Origin	Serogroup.sup.b	Inhibition by		Titer
			OspA	Growth	
B. burgdorferi					
B31	Tick, USA	1	+++	5,120	
297	CSF, USA	1	+++	5,120	
Sh.2.82.	USA		++	400	
B. afzelii					
PKo	Skin, Germany	2	+++	12,800	
PGau	Skin, Germany	2	+/-	.about.1:50.sup.c	
ACA I	Skin, Sweden	2	-	<1:50.sup.d	
B. ***garinii***					
PBr	CSF, Germany	3	+++	12,800	
PBi	CSF, Germany	4	++	800	
B4 91	Skin, Norway	?	-	<100.sup.d	
G2.22	CSF, Gennany	?	-	<50.sup.d	
***IP90***	Tick, Russia	X	-	<50.sup.d	
25015	Group.sup.a				
25015	Tick, USA	?	+/-	.about.1:25.sup.c	
.sup.a Phylogenetically distinct from B. burgdorferi sensu stricto (Casjens et.					

DETD . . . of the donors can be purified and systemically administered to a target population. Those individuals at high risk for developing \*\*\*borrelia\*\*\* infections include, but are limited to, patients in intensive care units, immunocompromised patients, surgery patients, children, and persons in areas . . . infestations such as the northeastern, midwestern, and western pacific United States. Two particular references which describe those at risk from \*\*\*borrelioses\*\*\* include Steere, 1994 and a report by the Centers for Disease Control, 1994.

DETD . . . that accessibility of DBP to antibodies is not an artifact of in vitro manipulation is to demonstrate passive protection from \*\*\*borrelia\*\*\* challenge with these antibodies. Even though common strains of inbred mice (such as C3H/HeJ, C3H/HeN, and BalblcByJ) may differ in the severity of disease elicited by \*\*\*borrelia\*\*\*, their sensitivities to infectious \*\*\*borrelia\*\*\* strains is more uniform. Additionally mouse-virulent stains Sh.2.82, N40, and B. afzelii PKo were also evaluated for their in vivo. . . FIG. 16H). At two weeks post-challenge tissue samples (bladder, heart, synovial fluid) were placed in BSKII medium and evidence of \*\*\*borrelial\*\*\* outgrowth from these tissues were assessed microscopically after 2 and 3 weeks of in vitro culture. Protection was judged to . . .

DETD . . . to infection. This suggests that an infection-induced memory response to OspA will be of little or no benefit. However, other \*\*\*borrelia\*\*\* surface proteins required for growth and persistence in vivo may not suffer this limitation as vaccine immunogens. Many bacterial pathogens including \*\*\*borrelia\*\*\* initiate infection following adhesion to specific macromolecules of the host target tissue. These adhesins are exposed at the bacterial surface. . .

DETD . . . favorable pharmacokinetics. The studies measured only infection

rather than disease, however, antibody levels which are not sufficient to eliminate all \*\*\*borrelia\*\*\* may in fact be sufficient to prevent disease pathologies.

DETD Isolation of Nucleic Acid Sequences Encoding DBPs from *B. burgdorferi*, *B. afzelii*, and *B. \*\*\*garinii\*\*\**

DETD Oligonucleotides were used as primers for PCRT.TM. amplifications of dbp gene fragments from \*\*\*borrelia\*\*\* strains representing the three major phylogenetic groups of Lyme disease spirochetes. Primers derived from the dbp gene of strain 297. . .

DETD Identification of candidate dbp alleles from *B. burgdorferi*, *B. afzelii*, and *B. \*\*\*garinii\*\*\** was accomplished using oligonucleotides diagrammed in FIG. 14 as primers for PCR.TM. amplifications of dbp gene fragments from \*\*\*borrelia\*\*\* strains representing the three major phylogenetic groups of Lyme disease spirochetes. Portions of the PCR.TM. amplification reactions were electrophoresed on. . .

DETD Table 9 shows a summary of the heterologous \*\*\*borrelia\*\*\* strain passive protection results discussed above. Data were compiled in tabular form and expressed as % of mice protected by. . .

DETD TABLE 7

Effect of Post-Challenge Passive Administration of Antisera on \*\*\*Borrelia\*\*\* Infection in C3H/HeJ Mice

Number of Mice Infected at Each Day of Serum Administration

Antiserum	0	2	4	7	10
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DETD TABLE 8

Amplification of a DBP Allele from Various \*\*\*Borrelia\*\*\* spp.

DBP	DBP	DBP	DBP	DBP
Full Length	Truncate	Pair 1	Pair 2	Pair

3

Species	Strain	Expected	564 bp	448. . .	+
	Sh.2.82	+	+	++	+
<i>B. afzelii</i>	ACA-1	+	-	-	-
	PGau	+	+	---	
<i>B. ***garinii***</i>	***IP90***		+	+	---
	B491	+	-	---	
	pBi	-	-	---	

DETD TABLE 9

Anti-DBP Serum	Anti-OspA Serum	Challenge Culture Positive Tissues	Culture Positive Tissues
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***Borrelia***	% of Mice	% of Mice
----------------	-----------	-----------

Strain	Bladder	Ear	Protected	Bladder	Ear	Protected
--------	---------	-----	-----------	---------	-----	-----------

*B. burgdorferi sensu stricto*

B31	0/5	0/5	100%	0/5	0/5	. . .
-----	-----	-----	------	-----	-----	-------

DETD Barthold et al., "Animal Model: Chronic Lyme \*\*\*borreliosis\*\*\* in the Laboratory Mouse," Am. J Pathol., 143:959-971, 1993.

DETD Barthold et al., "Kinetics of \*\*\*Borrelia\*\*\* burgdorferi

Dissemination and Evolution of Disease After Intradermal Inoculation of Mice," Am. J Pathol., 139:263-273, 1991.

DETD Barthold et al., "Lyme \*\*\*borreliosis\*\*\* in the Laboratory Mouse," In: Lyme Disease:

DETD Coburn et al., "Integrin .alpha..sub.IIb.beta..sub.3 Mediates Binding of the Lyme Disease Agent \*\*\*Borrelia\*\*\* burgdorferi to Human Platelets," Proc. Natl. Acad Sci. USA, 90:7059-7063, 1993.

DETD Duray, "Target Organs of \*\*\*Borrelia\*\*\* burgdorferi Infections:

Functional Responses and Histology," In: Lyme Disease: Molecular and Immunologic Approaches, S. E. Schutzer (ed.), Cold Spring Harbor. . .

DETD Haupl et al., "Persistence of \*\*\*Borrelia\*\*\* burgdorferi in Ligamentous Tissue From a Patient With Chronic Lyme \*\*\*borreliosis\*\*\*," Arthritis Rheum., 36:1621-1626, 1993.

DETD Isaacs, " \*\*\*Borrelia\*\*\* burgdorferi Bind to Epithelial Cell Proteoglycans," J. Clin Invest., 93:809-819, 1994.

DETD Zimmer et al., "Lyme Carditis in Immunodeficient Mice During Experimental Infection of \*\*\*Borrelia\*\*\* burgdorferi," Virchows Arch A Pathol. Anat., 417:129-135, 1990.

CLM What is claimed is:

31. The composition of claim 30, comprising a decorin binding protein or decorin binding peptide isolated from \*\*\*Borrelia\*\*\* .
32. The composition of claim 31, comprising a decorin binding protein or decorin binding peptide isolated from B. burgdorferi, B. japonica, B. \*\*\*garinii\*\*\* , or B. afzelii.
37. The bacterial protein of claim 36, wherein said bacterial protein is a B. burgdorferi, B. japonica, B. \*\*\*garinii\*\*\* , or B. afzelii bacterial protein.
46. A method for diagnosing a \*\*\*Borrelia\*\*\* infection, comprising: identifying within a clinical sample from an animal suspected of having such an infection: (i) a decorin binding. . .
47. The method of claim 46, comprising: identifying within a clinical sample from an animal suspected of having a \*\*\*Borrelia\*\*\* infection: (i) a decorin binding protein nucleic acid segment comprising a nucleic acid sequence of at least about 14 contiguous. . .
48. The method of claim 46, comprising: identifying within a clinical sample from an animal suspected of having a \*\*\*Borrelia\*\*\* infection: p2 (i) a decorin binding protein nucleic acid segment comprising a nucleic acid sequence of at least about 14. . .
49. The method of claim 46, comprising: identifying within a clinical sample from an animal suspected of having a \*\*\*Borrelia\*\*\* infection: (i) a decorin binding protein nucleic acid segment comprising a nucleic acid sequence of at least about 14 contiguous. . .
50. The method of claim 46, comprising: identifying within a clinical sample from an animal suspected of having a \*\*\*Borrelia\*\*\* infection: (i) a decorin binding protein nucleic acid segment comprising a nucleic acid sequence of at least about 14 contiguous. . .
51. The method of claim 46, comprising: identifying within a clinical sample from an animal suspected of having a \*\*\*Borrelia\*\*\* infection: (i) a decorin binding protein nucleic acid segment comprising a nucleic acid sequence of at least about 14 contiguous. . .
52. The method of claim 46, comprising: identifying within a clinical sample from an animal suspected of having a \*\*\*Borrelia\*\*\* infection: (i) a decorin binding protein nucleic acid segment comprising a nucleic acid sequence of at least about 14 contiguous. . .
53. The method of claim 46, comprising: identifying within a clinical sample from an animal suspected of having a \*\*\*Borrelia\*\*\* infection: (i) a decorin binding protein nucleic acid segment comprising a nucleic acid sequence of at least about 14 contiguous. . .
54. The method of claim 46, comprising: identifying within a clinical sample from an animal suspected of having a \*\*\*Borrelia\*\*\*

infection: (i) a decorin binding protein nucleic acid segment comprising a nucleic acid sequence of at least about 14 contiguous. . .  
55. The method of claim 46, comprising: identifying within a clinical sample from an animal suspected of having a \*\*\*Borrelia\*\*\* infection: (i) a decorin binding protein nucleic acid segment comprising a nucleic acid sequence of at least about 14 contiguous. . .  
56. The method of claim 46, wherein said \*\*\*Borrelia\*\*\* infection is a *B. burgdorferi*, *B. japonica*, *B. garinii*, or *B. afzelii* infection.

L15 ANSWER 9 OF 21 USPATFULL

AN 2001:67646 USPATFULL

TI Decorin binding protein compositions

IN Guo, Betty, Houston, TX, United States

Hook, Magnus, Houston, TX, United States

PA The Texas A & M University System, College Station, TX, United States  
(U.S. corporation)

PI US 6228835 B1 20010508

AI US 1998-221938 19981228 (9)

RLI Division of Ser. No. US 1996-589711, filed on 22 Jan 1996, now patented,  
Pat. No. US 5853987, issued on 29 Dec 1998 Continuation-in-part of Ser.  
No. US 1995-427023, filed on 24 Apr 1995, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Zitomer, Stephanie W.

LREP Williams, Morgan and Amerson

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN 25 Drawing Figure(s); 14 Drawing Page(s)

LN.CNT 4504

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\*Borrelia\*\*\* *burgdorferi*, the etiological agent of Lyme disease, and DNA segments encoding dbp from related \*\*\*borrelia\*\*\*. Also disclosed are decorin binding protein compositions and methods of use. The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathological \*\*\*Borrelia\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and anti-(decorin binding protein) antibodies will also be of use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\*Borrelia\*\*\* colonization in an animal. These DNA segments and the peptides derived therefrom are contemplated for use in the preparation of vaccines and, also, for use as carrier proteins in vaccine formulations, and in the formulation of compositions for use in the prevention of Lyme disease.

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\*Borrelia\*\*\* *burgdorferi*, the etiological agent of Lyme disease, and DNA segments encoding dbp from related \*\*\*borrelia\*\*\*. Also disclosed are decorin binding protein compositions and methods of use. The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathological \*\*\*Borrelia\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and. . . of

use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\*Borrelia\*\*\* colonization in an animal. These DNA segments and the peptides derived therefrom are contemplated for use in the preparation of. . .

SUMM . . . proteins derived from bacterial species. More particularly, the invention provides gene compositions encoding a decorin (Dcn) binding protein (DBP) from \*\*\*Borrelia\*\*\* burgdorferi and the corresponding peptide epitopes and protein sequences comprising native and synthetically-modified Dcn binding site domains. Various methods for. . .

SUMM Lyme disease (Steere, 1989), or Lyme \*\*\*borreliosis\*\*\*, is transmitted by ticks, particularly of the genus Ixodes, and caused by spirochetes of the genus \*\*\*Borrelia\*\*\*. Lyme disease agents, that is \*\*\*borrelia\*\*\* isolated from humans or animals with clinical Lyme disease, are currently classified into at least three phylogenetic groups: B. burgdorferi sensu stricto, B. \*\*\*garinii\*\*\*, and B. afzelii. Strains potentially representing other phylogenetic groups of Lyme disease agents as well, such as group 25015, have. . .

SUMM . . . vitro-grown or tick-borne B. burgdorferi. Based largely on the protective efficacy of experimental OspA vaccines in rodent models of Lyme \*\*\*borreliosis\*\*\*, three monovalent OspA-based vaccines are currently in clinical trials. However, recent findings suggest that broad, sustained protection of humans may. . .

SUMM c) OspA is serologically diverse, particularly among European and Asian B. \*\*\*garinii\*\*\* and B. afzelii isolates. Reactivity with panels of OspA monoclonal antibodies (mAbs), and DNA sequence analysis has shown that as. . .

SUMM . . . and Bockenstedt, 1993). OspA is expressed by B. burgdorferi within ticks (Barbour et al., 1983), but detection of OspA on \*\*\*borrelia\*\*\* in tissue early after infection is difficult. Passive immunization of mice with OspA antibody (Schaible et al., 1990), or immunization. . .

SUMM . . . vivo only at later stages when the infection becomes disseminated. This would be explained by down-regulation of OspA expression by \*\*\*borrelia\*\*\* shortly after initiation of feeding by the tick.

SUMM Modulation of \*\*\*borrelia\*\*\* antigen expression within feeding ticks has recently been reported for OspC; initially low in resting ticks, OspC levels increase on. . .

SUMM . . . to pre-exist at high levels in human or animal hosts prior to the tick bite to be effective against OspA-expressing \*\*\*borrelia\*\*\* in the tick, and may receive little or no boosting upon delivery of the spirochetes into the skin within the. . .

SUMM . . . the gut of the infecting tick, before inoculation of the pathogen." Consistent with this hypothesis it has been shown that anti- \*\*\*borrelia\*\*\* serum can protect mice from infection by tick bite if administered within two days after initiation of feeding by \*\*\*borrelia\*\*\* -infected ticks, but not when passively administered at later times (Shih et al., 1995). The antibody levels in response to recombinant. . .

SUMM . . . the host cell ECM component, Dcn. Also disclosed are methods for active and passive immunization against B. burgdorferi and related \*\*\*borrelia\*\*\* including B. afzelii and B. \*\*\*garinii\*\*\* using novel native and site-specifically-altered DBP compositions and

DBP-derived epitopic peptides from *B. burgdorferi*, *B. afzelii* and *B. \*\*\*garinii\*\*\**. Particular aspects of the invention relate to novel nucleic acid segments encoding these peptides and epitopes, and methods for the. . .

SUMM SEQ ID NO:1 comprises the complete nucleotide sequence of a 2.5 kb insert of *\*\*\*borrelia\*\*\** genomic DNA cloned in the pBlueScript.TM. vector. This recombinant clone, designated BG26:pB/2.5(5), has been deposited with the American Type Culture. . .

SUMM . . . DBPs. Strain variants are those nucleic acid compositions and polypeptide compositions expressed by various strains of *B. burgdorferi* and related *\*\*\*borrelas\*\*\** including *B. afzelii* and *B.*

*\*\*\*garinii\*\*\** which specifically encode DBPs. These DBPs also bind Dcn and related proteoglycans and share similarity of structure and function with. . .

SUMM . . . alternatively by the demonstrating the ability of the strain-variant DBP to lessen or prevent adherence of *B. burgdorferi* and related *\*\*\*borrelas\*\*\** including *B. afzelii* and *B. \*\*\*garinii\*\*\** to Dcn.

SUMM . . . be used, so long as the coding segment employed encodes a protein or peptide of interest (e.g., a DBP from *\*\*\*Borrelia\*\*\**, and particularly a DBP from *B. burgdorferi*, *B. afzelii*, or *B.*

*\*\*\*garinii\*\*\**, and does not include any coding or regulatory sequences that would have an adverse effect on cells. Therefore, it will. . .

SUMM . . . that it will direct the expression and production of the protein or peptide epitope of interest (e.g., a DBP from

*\*\*\*Borrelia\*\*\** and in particular, from *B. burgdorferi*, *B. afzelii*, *B. \*\*\*garinii\*\*\**, or *B. japonica*) when incorporated into a host cell. In a recombinant expression vector, the coding portion of the DNA. . .

SUMM . . . anti-DBP antibodies for diagnostic and therapeutic methods relating to the detection and treatment of infections caused by *B. burgdorferi* and related- *\*\*\*borrelas\*\*\**-including *B. afzelii* and *B. \*\*\*garinii\*\*\**.

SUMM . . . The nucleic acid sequences encoding DBP are useful as diagnostic probes to detect the presence of *B. burgdorferi*, and related *\*\*\*borrelas\*\*\** including *B. afzelii* and *B. \*\*\*garinii\*\*\** in a test sample, using conventional techniques. In one such method of diagnosing *\*\*\*Borrelial\*\*\** infection, dbp nucleic acid segments may be used in Southern hybridization analyses or Northern hybridization analyses to detect the presence. . .

SUMM . . . serum concentration of DBP-reactive- antibodies that is at least twice that required for inhibition of in vitro growth of endemic *\*\*\*borrelia\*\*\** strains. It is contemplated that the duration of dosing maintaining anti-DBP levels at these inhibitory antibody concentrations would be for. . .

SUMM . . . length will often be preferred., The antigenic proteins or peptides may also be combined with other agents, such as other *\*\*\*borrelial\*\*\** peptide or nucleic acid compositions, if desired.

SUMM . . . methods for the stimulation of an immune response include vaccination regimens designed to prevent or lessen significant infections caused by *\*\*\*borrelas\*\*\** or other bacteria expressing a DBP, and treatment regimens that may lessen the severity or duration of any infection, it. . . treatment methods may be used particularly for the treatment of infections caused by pathogens such as *B. burgdorferi*, *B. afzelii*, *B. \*\*\*garinii\*\*\**, related *\*\*\*borrelial\*\*\** species, and other bacteria which express DBPs and adhere to Dcn.

SUMM Immunoformulations of this invention, whether intended for vaccination, treatment, or for the generation of antibodies useful in the detection of \*\*\*borrelia\*\*\* and in particular B. burgdorferi, the prevention of bacterial adhesion, or in the case of bacterial colonization, promotion of bacterial. . .

SUMM . . . in the immunodetection of compounds, present within clinical samples, that are indicative of Lyme disease or related infections caused by \*\*\*borrelia\*\*\* , and in particular B. burgdorferi. The kits may also be used in antigen or antibody purification, as appropriate.

SUMM . . . even perhaps urine samples may be employed. This allows for the diagnosis of Lyme disease and related infections caused by \*\*\*borrelia\*\*\* , and in particular, B. burgdorferi. Furthermore, it is contemplated that such embodiments may have application to non-clinical samples, such as. . .

SUMM . . . and peptides, in particular those DBP proteins isolated from prokaryotic sources, and particularly bacteria. DNA segments isolated from species of \*\*\*Borrelia\*\*\* and related bacteria which are shown to bind Dcn are particularly preferred for use in the methods disclosed herein. Such. . .

SUMM . . . particularly contemplated to be useful in the production of Anti-DBP antibodies for use in passive immunization methods for prevention of \*\*\*borrelia\*\*\* adhesion to Dcn, and treatment of infections due to \*\*\*Borrelia\*\*\* invasion, and particularly invasion by B. burgdorferi.

SUMM . . . vaccine compositions useful in the prevention of Lyme disease and antibody compositions useful in the prevention of Dcn binding to \*\*\*Borrelia\*\*\* .

SUMM . . . bacterial cells. These aspects provide methods and compositions for producing bacterial colonization of an animal host with attenuated, or avirulent \*\*\*Borrelia\*\*\* expressing cell surface DBP epitopes.

SUMM . . . with an antibody composition disclosed herein, and detecting the formation of immune complexes. In preferred embodiments, the bacterium is a \*\*\*borrelia\*\*\* , and most preferably, a B. burgdorferi, B. afzelii, or B. \*\*\*garinii\*\*\* strain.

SUMM . . . include pharmaceutically-acceptable formulations of either the antibodies or peptide antigens disclosed herein. Such kits are useful in the detection of \*\*\*borrelia\*\*\* in clinical samples, and also useful for inhibiting or promoting the binding of \*\*\*borrelia\*\*\* to the ECM component, Dcn. In preferred embodiments, the bacteria detected using such kits include \*\*\*borrelia\*\*\* , and in particular, B. burgdorferie, B. afzelii, B. \*\*\*garinii\*\*\* , or related species.

SUMM Other aspects of the invention include methods of inhibiting bacterial colonization, and particularly colonization by \*\*\*borrelia\*\*\* , in an animal by administering to the animal an antibody of the present invention which prevents or significantly reduces the. . . the antibody composition may be prophylactically prior to and/or following diagnosis of Lyme disease or other multisystemic disorders caused by \*\*\*Borrelioses\*\*\* which may involve the skin, joints, heart, and central nervous system. The administration may also be made in passive immunization. . .

SUMM . . . other Gram-negative hosts including various Pseudomonas species may be used in the recombinant expression of the genetic constructs disclosed herein. \*\*\*Borrelia\*\*\* themselves may be used to express these constructs, and in particular, B. burgdorferi, B. afzelii, B.

japonica and B. \*\*\*garinii\*\*\* . DRWD . . . tissue samples (bladder, FIG. 12A; ear, FIG. 12B; and joint, FIG. 12C) were placed in BSKII medium and evidence of \*\*\*borrelial\*\*\* outgrowth from these tissues was assessed microscopically after 2 wk of in vitro culture at 34.degree. C.; 10-20 high power fields of samples of the cultures were examined before judging tissues to be uninfected. The number of visible \*\*\*borrelia\*\*\* per microscopic field in organ cultures from each mouse are shown. Bladder tissue is a very sensitive indicator of \*\*\*borrelial\*\*\* infection, while joint and skin are also sources of \*\*\*borrelial\*\*\* infection, thus all three tissue samples were routinely assayed. Complete protection was judged when no spirochetes were recoverable from all three tissue sites. Partial or intermediate detection was determined when no \*\*\*borrelia\*\*\* were detectable in joint and skin samples, but a few remaining bacteria were present in bladder tissue.

DRWD FIG. 13. Membrane localization of candidate \*\*\*borrelia\*\*\* vaccine antigens. B. burgdorferi. B31 total membranes were separated into inner-(IM, lane 2) and outer-membranes (OM, lane 4) using . . . by others (Bledsoe et al., 1994). By detergent phase portioning DBP appears to be amphiphilic as are OspA and other \*\*\*borrelia\*\*\* membrane lipoproteins (Brandt et al., 1990).

DRWD . . . Five combinations of these oligonucleotides were used as primer pairs for PCR.TM. amplification studies with genomic DNA templates from various \*\*\*borrelia\*\*\* strains. The sizes, in base pairs, of the dbp gene segments expected, based on the strain 297 sequence, from these. . .

DETD . . . is anticipated to be especially effective in treatment regimens for Lyme disease, and as a cost-effective prophylaxis for prevention of \*\*\*borrelial\*\*\* infections.

DETD . . . limitations of the prior art, particularly with respect to OspA and other antigens previously investigated as antigens for development of \*\*\*borrelia\*\*\* vaccines. Indeed, vaccine compositions comprising DBPs are likely to be superior to those previously available containing OspA alone.

DETD . . . of OspA as antibodies reactive with DBP derived from B. burgdorferi sensu stricto are also growth-inhibitory to strains of B. \*\*\*garinii\*\*\* and B. afzelii.

DETD Anti-DBP Antibodies Eliminate \*\*\*Borrelia\*\*\* From Infected Animals  
DETD dbp Nucleic Acid Segments Useful in Identifying \*\*\*Borrelial\*\*\* Isolates

DETD . . . and isolate molecular clones of alleles of this gene present in different phylogenetic groups of Lyme disease spirochetes including B. \*\*\*garinii\*\*\* and B. afzelii by utilization of such techniques as PCR.TM..

DETD . . . kDa. However, due to the copurification of the DBP with other B. burgdorferi proteins, complete purification of native DBP from \*\*\*borrelia\*\*\* in pure form has not been achieved.

DETD . . . antibodies to gene products encoded by such nucleic acid segments, or in the production of diagnostic and treatment protocols for \*\*\*borrelia\*\*\* infection, and in particular, infection with B. burgdorferi, B. afzelii, or B. \*\*\*garinii\*\*\* , and those infections leading to Lyme disease. Any and all such combinations are intended to fall within the scope of. . .

DETD . . . from which the DBP composition may be applied to a tissue site, skin lesion, wound area, or other site of \*\*\*borrelial\*\*\* infection.

However, the single container means may contain a dry, or lyophilized, mixture of a DBP composition, which may or . . .  
DETD . . . analyze the distribution of bacteria expressing DBPs during cellular -infection, for example, to determine the cellular or tissue-specific distribution of \*\*\*borrelia\*\*\* under different physiological conditions. A particularly useful application of such antibodies is in purifying native or recombinant DBPs, for example, . . .

DETD DBP Compositions for Treating \*\*\*Borrelia\*\*\* Infections  
DETD . . . quantities. The selected antigens, and variants thereof, are proposed to have significant utility in diagnosing and treating infections cause by \*\*\*borrelia\*\*\* and in particular, B. burgdorferi, B. garinii\*\*\* and B. afzelii. For example, it is proposed that rDBPs, peptide variants thereof, and/or antibodies against such rDBPs may also be used in immunoassays to detect \*\*\*borrelia\*\*\* or as vaccines or immunotherapeutics to treat \*\*\*borrelia\*\*\* infections, and to prevent bacterial adhesion to ECM components such as Dcn in the same manner as native DBP compositions.

DETD The peptides provided by this invention are ideal targets for use as vaccines or immunoreagents for the treatment of various \*\*\*borrelia\*\*\* -related diseases, and in particular, those caused by species which contain DBP and DBP-encoding genes, and hence those which express either. . .

DETD The \*\*\*Borrelia\*\*\* binding site on the Dcn molecule has not been identified. Presumably, Dcn binds both collagen and \*\*\*borrelia\*\*\* at once, with the two interactions involving different sites on the proteoglycan. The requirement of intact Dcn adhesin on the. . .

DETD . . . adhesive function of DBP, and its role as a target for growth-inhibitory antibodies, imply that DBP is localized to the \*\*\*borrelia\*\*\* outer membrane. To provide additional biochemical support for this B. burgdorferi B3 total membranes were separated into inner and outer. . . (Bledsoe et al., 1994). By detergent phase portioning DBP appears to be amphiphilic (FIG. 13) as are OspA and other \*\*\*borrelia\*\*\* membrane lipoproteins (Brandt et al., 1990). To confirm the presence of lipid on these proteins B. burgdorferi B31 was metabolically. . .

DETD Identification of DBPs in \*\*\*borrelia\*\*\* Isolates

DETD One aspect of the present invention, is the identification of \*\*\*borrelia\*\*\* using the DBP compositions disclosed herein as diagnostic indicators of \*\*\*borrelia\*\*\* infection. As shown in Table 2, an assay of DBP in \*\*\*borrelia\*\*\* using Western hybridization analyses, it was possible to identify the presence of DBPs in at least 13 strains of B. burgdorferi, 5 strains of B. garinii\*\*\*, and at least three strains of B. afzelii. These methods represent important diagnostic tools for the identification of bacteria in. . .

#### DETD TABLE 2

#### Assay of DBP in \*\*\*borrelia\*\*\* By Western Blot

Strain	Origin	DBP	Source
<b>B. burgdorferi</b>			
N40	tick	+	S. Norris
N40	tick	+	S. Norris
Sh2. . .	skin	+	J. Leong
G39/40	tick	+	J. Leong
297	CSF	+	R. Isaacs

25015 tick + M. Hanson  
B. \*\*\*garinii\*\*\*  
PBi CSF + J. Leong  
PBi CSF + J. Leong  
G2 CSF + J. Leong  
PBr CSF + M. Hanson  
B4-91 CSF + M. Hanson  
\*\*\*Ip90\*\*\* tick + M. Hanson

B. afzelii  
PKo skin + M. Hanson  
ACA1 skin + M. Hanson  
PGau skin + M. . .

DETD DBP Compositions Block Adherence of \*\*\*borrelia\*\*\* to Decorin  
DETD Inhibitory Activity of anti-rDBP Serum Towards in vitro Growth of  
\*\*\*Borrelia\*\*\* Strains of Diverse Origin

DETD Two other \*\*\*borrelia\*\*\* proteins, OspA and OspB, believed to be surface-exposed have been shown to be targets for bacterial killing by specific antibodies. . . protein's exposure at the surface of a cell. Rabbit antisera were serially diluted in 96 well plates, 10.sup.5 mid-log phase \*\*\*borrelia\*\*\* in BSK II medium were added per well, the mixture was incubated for three days, and cell viability (motility) was. . . anti-rOspA serum, used as a positive control, to about 1:50,000 for B. burgdorferi sensu stricto strains including the homologous strain 297. \*\*\*Borrelia\*\*\* incubated in serum raised against a Streptococcus pneumoniae protein, PspA, were fully motile. Significantly, serum raised against DBP from B. . .

DETD . . . of the donors can be purified and systemically administered to a target population. Those individuals at high risk for developing \*\*\*borrelia\*\*\* infections include, but are limited to, patients in intensive care units, immunocompromised patients, surgery patients, children, and persons in areas. . . infestations such as the northeastern, midwestern, and western pacific United States. Two particular references which describe those at risk from \*\*\*borrelioses\*\*\* include Steere, 1994 and a report by the Centers for Disease Control, 1994.

DETD At two weeks post-challenge tissue samples (bladder, heart, synovial fluid) are placed in BSKII medium and evidence of \*\*\*borrelial\*\*\* outgrowth from these tissues is assessed microscopically after 2 and 3 wk of in vitro culture. Protection is judged to. . .

DETD . . . that accessibility of DBP to antibodies is not an artifact of in vitro manipulation is to demonstrate passive protection from \*\*\*borrelia\*\*\* challenge with these antibodies. Even though common strains of inbred mice (such as C3H/HeJ, C3H/HeN, and Balb/cByJ, Barthold et al., 1993) may differ in the severity of disease elicited by \*\*\*borrelia\*\*\*, their sensitivities to infectious \*\*\*borrelia\*\*\* strains is more uniform.

DETD . . . (Sadziene et al., 1993) (Table 7). Rabbit antisera were serially diluted in 96-well plates in 0.1 ml BSKII medium, 10.sup.5 \*\*\*borrelia\*\*\* in the mid-log phase of growth in 0.1 ml BSKII medium were added per well, the mixture was incubated for. . . into at least four OspA serogroups, and have diverse geographic origins. Serum against an irrelevant antigen, PspA, was not inhibitory. \*\*\*Borrelia\*\*\* strains were obtained from the laboratories of Drs. Steve Norris, John Leong, Alan Barbour, Robert Lane, Robin Isaacs, David Dorward, . . .

DETD Identification of candidate dbp alleles from B. burgdorferi, B. afzelii,

and B. \*\*\*garinii\*\*\* was accomplished using oligonucleotides diagrammed in FIG. 14 as primers for PCR.TM. amplifications of dbp gene fragments from \*\*\*borrelia\*\*\* strains representing the three major phylogenetic groups of Lyme disease spirochetes. Portions of the PCR.TM. amplification reactions were electrophoresed on. . .

DETD . . . to infection. This suggests that an infection-induced memory response to OspA will be of little or no benefit. However, other \*\*\*borrelia\*\*\* surface proteins required for growth and persistence in vivo may not suffer this limitation as vaccine immunogens. Many bacterial pathogens including \*\*\*borrelia\*\*\* initiate infection following adhesion to specific macromolecules of the host target tissue. These adhesins are exposed at the bacterial surface. . .

DETD . . . favorable pharmacokinetics. The studies measured only infection rather than disease, however, antibody levels which are not sufficient to eliminate all \*\*\*borrelia\*\*\* may in fact be sufficient to prevent disease pathologies.

DETD Isolation of Nucleic Acid Sequences Encoding DBPs from B. burgdorferi, B. afzelii , and B. \*\*\*garinii\*\*\*

DETD Oligonucleotides diagrammed in FIG. 14 were used as primers for PCR.TM. amplifications of dbp gene fragments from \*\*\*borrelia\*\*\* strains representing the three major phylogenetic groups of Lyme disease spirochetes. Primers derived from the dbp gene of strain 297. . .

#### DETD TABLE 6

##### In vitro Growth Inhibitory Activity of Rabbit

##### Anti-rDB.sub.297 Serum Against Diverse \*\*\*Borrelia\*\*\* Strains

##### Growth Inhibition by

##### Anti-rDBP.sub.297

OspA	Growth		
Strain	Origin	Serogroup.sup.b	Inhibition Titer
<i>D. burgdorferi</i>			
B31	Tick, USA	1	+++ 5,120
297	CSF, USA	1 . . . 1	+++ 5,120
<i>B. afzelii</i>			
PKo	Skin, Germany	2	+++ 12,800
PGau	Skin, Germany	2	+/- .about.1:50.sup.c
ACA I	Skin, Sweden	2	- <1:50.sup.d
<i>B. ***garinii***</i>			
PBr	CSF, Germany	3	+++ 12,800
PBi	CSF, Germany	4	++ 800
B4 91	Skin, Norway	?	- <100.sup.d
G2.22	CSF, Germany	?	- <50.sup.d
***Ip90***		Tick, Russia X	- <50.sup.d
25015	Group.sup.a Tick, USA	?	+/- .about.1:25.sup.c
25015	.sup.a Phylogenetically distinct from <i>B. burgdorferi</i> sensu stricto: Casjens et.		

#### DETD TABLE 7

##### Effect of Post-Challenge Passive Administration of

##### Antisera on \*\*\*Borrelia\*\*\* Infection in C3H/HeJ Mice

##### Number of Mice Infected at Each Day of Serum Administration

Antiserum 0	2	4	7	10
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#### DETD TABLE 8

##### Amplification of a DBP Allele from Various \*\*\*Borrelia\*\*\* Species

		DBP	DBP	DBP	DBP	DBP
		Full Length	Truncate	Pair 1	Pair 2	Pair
3						
Species	Strain	Expected	564 bp	448.	..	+
	SH2	+	+	+	+	+
B. afzelli	ACA-1		+	-	-	-
	pGAU	+	+	---		
B.	***garinii***	***IP90***		+	+	---
	B491	+	-	---		
	pBi	-	-	---		
DETD	Barthold et al., "Animal Model: Chronic Lyme ***borreliosis*** in the Laboratory Mouse," Am. J. Pathol., 143:959-971, 1993.					
DETD	Barthold et al., "Kinetics of ***Borrelia*** burgdorferi Dissemination and Evolution of Disease After Intradermal Inoculation of Mice," Am. J. Pathol., 139:263-273, 1991.					
DETD	Barthold et al., "Lyme ***borreliosis*** in the Laboratory Mouse," In: Lyme Disease: Molecular and Immunology Approaches, S. E. Schutzer (ed.), Cold Spring Harbor Press, Plainview, . . .					
DETD	Coburn et al., "Integrin .alpha..sub.IIb.beta..sub.3 Mediates Binding of the Lyme Disease Agent ***Borrelia*** burgdorferi to Human Platelets," Proc. Natl. Acad. Sci. USA, 90:7059-7063, 1993.					
DETD	Duray, "Target Organs of ***Borrelia*** burgdorferi Infections: Functional Responses and Histology," In: Lyme Disease: Molecular and Immunologic Approaches, S. E. Schutzer (ed.), Cold Spring Harbor. . .					
DETD	Haupl et al., "Persistence of ***Borrelia*** burgdorferi in Ligamentous Tissue From a Patient With Chronic Lyme ***borreliosis***," Arthritis Rheum., 36:1621-1626, 1993.					
DETD	Isaacs, " ***Borrelia*** burgdorferi Bind to Epithelial Cell Proteoglycans," J. Clin. Invest., 93:809-819, 1994.					
DETD	Zimmer et al., "Lyme Carditis in Immunodeficient Mice During Experimental Infection of ***Borrelia*** burgdorferi," Virchows Arch. A Pathol. Anat., 417:129-135, 1990.					
CLM	What is claimed is:					
8.	The protein or peptide of claim 7, wherein said protein or peptide is a ***Borrelia*** decorin binding protein or peptide.					
9.	The protein or peptide of claim 8, wherein said protein or peptide is a B. burgdorferi, B. ***garinii*** , or B. afzelii decorin binding protein or peptide.					
13.	The protein of claim 12, wherein said bacterial protein is a ***Borrelia*** bacterial protein.					
14.	The protein of claim 13, wherein said bacterial protein is a B. burgdorferi, B. ***garinii*** , or B. afzelii bacterial protein.					

L15 ANSWER 10 OF 21 CABA COPYRIGHT 2002 CABI

AN 2001:79893 CABA

DN 20013070519

TI P13, an integral membrane protein of \*\*\*Borrelia\*\*\* burgdorferi, is C-terminally processed and contains surface-exposed domains

AU Noppa, L.; Ostberg, Y.; Lavrinovich, M.; Bergstrom, S.

CS Department of Microbiology, Umea University, SE-901 87 Umea, Sweden.

SO Infection and Immunity, (2001) Vol. 69, No. 5, pp. 3323-3334. 52 ref.

ISSN: 0019-9567

DT Journal

LA English

AB To elucidate antigens present on the bacterial surface of \*\*\*Borrelia\*\*\* burgdorferi sensu lato that may be involved in pathogenesis, we characterized a protein, P13, with an apparent molecular mass of 13 kDa. The protein was immunogenic and was expressed in large amounts during in vitro cultivation compared to other known antigens. An immunofluorescence assay, immunoelectron microscopy, and protease sensitivity assays indicated that P13 is surface exposed. The deduced sequence of the P13 peptide revealed a possible signal peptidase type I cleavage site, and computer analysis predicted that P13 is an integral membrane protein with 3 transmembrane-spanning domains. Mass spectrometry, in vitro translation, and N- and C-terminal amino acid sequencing analyses indicated that P13 was posttranslationally processed at both ends and modified by an unknown mechanism. Furthermore, p13 belongs to a gene family with 5 additional members in B. burgdorferi sensu stricto. The p13 gene is located on the linear chromosome of the bacterium, in contrast to 5 paralogous genes, which are located on extrachromosomal plasmids. The size of the p13 transcript was consistent with a monocistronic transcript. This new gene family may be involved in functions that are specific for this spirochaete and its pathogenesis. The nucleotide sequences reported in this paper were submitted to the GenBank database and were assigned the following accession numbers: B. burgdorferi B31 and B313, AF085739; B. afzelii ACA1, AF085740; and B. \*\*\*garinii\*\*\* \*\*\*Ip90\*\*\* , AF085741.

TI P13, an integral membrane protein of \*\*\*Borrelia\*\*\* burgdorferi, is C-terminally processed and contains surface-exposed domains.

AB To elucidate antigens present on the bacterial surface of \*\*\*Borrelia\*\*\* burgdorferi sensu lato that may be involved in pathogenesis, we characterized a protein, P13, with an apparent molecular mass of . . . database and were assigned the following accession numbers: B. burgdorferi B31 and B313, AF085739; B. afzelii ACA1, AF085740; and B. \*\*\*garinii\*\*\* \*\*\*Ip90\*\*\* , AF085741.

BT \*\*\*Borrelia\*\*\* ; Spirochaetaceae; Spirochaetales; Gracilicutes; bacteria; prokaryotes

ORGN \*\*\*Borrelia\*\*\* burgdorferi

L15 ANSWER 11 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

3

AN 2001:151398 BIOSIS

DN PREV200100151398

TI 66 kDa antigen from \*\*\*Borrelia\*\*\* .

AU Bergstrom, Sven (1); Barbour, Alan George

CS (1) Umea Sweden

ASSIGNEE: Symbicom AB, Umea, Sweden

PI US 6090586 July 18, 2000

SO Official Gazette of the United States Patent and Trademark Office Patents, (July 18, 2000) Vol. 1236, No. 3, pp. No Pagination. e-file.

ISSN: 0098-1133.

DT Patent

LA English

AB The present invention relates to nucleic acid molecules, polypeptides encoded by the same, antibodies directed thereto and a method of preparing such polypeptides including: (a) inserting an isolated DNA molecule coding for a polypeptide which is immunoreactive with a 66 kDa polypeptide

derived from \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* into an expression vector; (b) transforming a host organism or cell with the vector; (c) culturing the transformed host cell under suitable conditions; and (d) harvesting the polypeptide. The isolated DNA molecule is preferably at least 10 nucleotides in length, and the method may optionally include subjecting the polypeptide to post-translational modification. The host cell can be a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism such as a fungus, an insect cell, a plant cell, or a mammalian cell.

TI 66 kDa antigen from \*\*\*Borrelia\*\*\* .

AB. . . (a) inserting an isolated DNA molecule coding for a polypeptide which is immunoreactive with a 66 kDa polypeptide derived from \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* into an expression vector; (b) transforming a host organism or cell with the vector; (c) culturing the transformed host cell. . .

IT . . .

Immune System (Chemical Coordination and Homeostasis); Methods and Techniques; Pharmacology

IT Diseases

Lyme disease: bacterial disease

IT Chemicals & Biochemicals

\*\*\*Borrelia\*\*\* 66 kDa antigen: diagnostic agent, vaccine; nucleic acid: fragments; polypeptides

IT Alternate Indexing

Lyme Disease (MeSH)

ORGN Super Taxa

Spirochaetaceae: Spirochaetales, Spirochetes, Eubacteria, Bacteria, Microorganisms

ORGN Organism Name

\*\*\*Borrelia\*\*\* (Spirochaetaceae): pathogen

ORGN Organism Superterms

Bacteria; Eubacteria; Microorganisms

L15 ANSWER 12 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

4

AN 2001:56265 BIOSIS

DN PREV200100056265

TI 66 kDa antigen from \*\*\*Borrelia\*\*\* .

AU Bergstrom, Sven (1); Barbour, Alan George

CS (1) Umea Sweden

ASSIGNEE: Symbicom AB, Ulmea, Sweden

PI US 6068842 May 30, 2000

SO Official Gazette of the United States Patent and Trademark Office Patents, (May 30, 2000) Vol. 1234, No. 5, pp. No Pagination. e-file.

ISSN: 0098-1133.

DT Patent

LA English

AB The present invention relates to nucleic acid molecules, polypeptides encoded by the same, antibodies directed thereto and a method of preparing such polypeptides including: (a) inserting an isolated DNA molecule coding for a polypeptide which is immunoreactive with a 66 kDa polypeptide derived from \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* into an expression vector; (b) transforming a host organism or cell with the vector; (c) culturing the transformed host cell under suitable conditions; and (d) harvesting the polypeptide. The isolated DNA molecule is

preferably at least 10 nucleotides in length, and the method may optionally include subjecting the polypeptide to post-translational modification. The host cell can be a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism such as a fungus, an insect cell, a plant cell, or a mammalian cell.

TI 66 kDa antigen from \*\*\*Borrelia\*\*\* .

AB. . . (a) inserting an isolated DNA molecule coding for a polypeptide which is immunoreactive with a 66 kDa polypeptide derived from \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* into an expression vector; (b) transforming a host organism or cell with the vector; (c) culturing the transformed host cell. . .

ORGN Super Taxa

Spirochaetaceae: Spirochaetales, Spirochetes, Eubacteria, Bacteria, Microorganisms

ORGN Organism Name

\*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* (Spirochaetaceae): strain-  
\*\*\*IP90\*\*\*

ORGN Organism Superterms

Bacteria; Eubacteria; Microorganisms

L15 ANSWER 13 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

5

AN 2000:465321 BIOSIS

DN PREV200000465321

TI 66 kDa antigen from \*\*\*Borrelia\*\*\* .

AU Bergstrom, Sven (1); Barbour, Alan George

CS (1) Umea Sweden

ASSIGNEE: Symbicom AB, Umea, Sweden

PI US 6054296 April 25, 2000

SO Official Gazette of the United States Patent and Trademark Office Patents,  
(Apr. 25, 2000) Vol. 1233, No. 4, pp. No pagination. e-file.

ISSN: 0098-1133.

DT Patent

LA English

AB The present invention relates to nucleic acid molecules, polypeptides encoded by the same, antibodies directed thereto and a method of preparing such polypeptides including: (a) inserting an isolated DNA molecule coding for a polypeptide which is immunoreactive with a 66 kDa polypeptide derived from \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* into an expression vector; (b) transforming a host organism or cell with the vector; (c) culturing the transformed host cell under suitable conditions; and (d) harvesting the polypeptide. The isolated DNA molecule is preferably at least 10 nucleotides in length, and the method may optionally include subjecting the polypeptide to post-translational modification. The host cell can be a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism such as a fungus, an insect cell, a plant cell, or a mammalian cell.

TI 66 kDa antigen from \*\*\*Borrelia\*\*\* .

AB. . . (a) inserting an isolated DNA molecule coding for a polypeptide which is immunoreactive with a 66 kDa polypeptide derived from \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* \*\*\*IP90\*\*\* into an expression vector; (b) transforming a host organism or cell with the vector; (c) culturing the transformed host cell. . .

IT Major Concepts

Biochemistry and Molecular Biophysics

IT Chemicals & Biochemicals

\*\*\**Borrelia*\*\*\* 66-kiloDalton antigen; DNA; nucleic acid;  
polypeptides

ORGN Super Taxa

Spirochaetaceae: Spirochaetales, Spirochetes, Eubacteria, Bacteria,  
Microorganisms

ORGN Organism Name

\*\*\**Borrelia*\*\*\* \*\*\*garinii\*\*\* (Spirochaetaceae)

ORGN Organism Superterms

Bacteria; Eubacteria; Microorganisms

L15 ANSWER 14 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2000:360663 BIOSIS

DN PREV200000360663

TI Differentiation of \*\*\**Borrelia*\*\*\* *burgdorferi* sensu lato on the basis  
of RNA polymerase gene (*rpoB*) sequences.

AU Lee, Seung-Hyun; Kim, Bum-Joon; Kim, Jong-Hyun; Park, Kyung-Hee; Kim,  
Seo-Jeong; Kook, Yoon-Hoh (1)

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DT Article

LA English

SL English

AB We determined the nucleotide sequences (329 bp) of the *rpoB* DNAs from 22  
reference strains of \*\*\**Borrelia*\*\*\*. No insertions or deletions were  
observed. Deduced amino acid sequences of amplified *rpoB* DNA comprised 109  
amino acid residues (N450 to M558 (Escherichia coli numbering)). All amino  
acid sequences were identical with the exception of those of

\*\*\**Borrelia*\*\*\* *lusitaniae* PotiB2 (T461fwdarwA) and *B. bissettii* DN127  
(I498fwdarwV).

Each species of *B. burgdorferi* sensu lato was  
differentiated as a distinct entity in the phylogenetic tree constructed  
by a neighbor-joining method. *B. burgdorferi* sensu lato could be  
distinguished from *B. turicatae* and *B. hermsii*, which are associated with  
relapsing fever. Seventeen Korean isolates could be identified by  
PCR-linked direct sequencing and restriction analysis of the *rpoB* DNA.  
These results suggest that *rpoB* DNA is useful for identification and  
characterization of \*\*\**Borrelia*\*\*\*. In addition, we developed the  
rapid species identification method using the species-specific primer sets  
based on *rpoB* gene sequences.

TI Differentiation of \*\*\**Borrelia*\*\*\* *burgdorferi* sensu lato on the basis  
of RNA polymerase gene (*rpoB*) sequences.

AB We determined the nucleotide sequences (329 bp) of the *rpoB* DNAs from 22  
reference strains of \*\*\**Borrelia*\*\*\*. No insertions or deletions were  
observed. Deduced amino acid sequences of amplified *rpoB* DNA comprised 109  
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rapid species identification method using the species-specific primer sets

based on rpoB gene sequences.

IT Major Concepts

Molecular Genetics (Biochemistry and Molecular Biophysics)

IT Chemicals & Biochemicals

RNA polymerase; \*\*\**Borrelia*\*\*\* *afzelii* rpoB gene (Spirochaetaceae);

\*\*\**Borrelia*\*\*\* *andersonii* rpoB gene (Spirochaetaceae);

\*\*\**Borrelia*\*\*\* *bissettii* rpoB gene (Spirochaetaceae);

\*\*\**Borrelia*\*\*\* *burgdorferi* rpoB gene (Spirochaetaceae);

\*\*\**Borrelia*\*\*\* \*\*\**garinii*\*\*\* rpoB gene (Spirochaetaceae);

\*\*\**Borrelia*\*\*\* *hermsii* rpoB gene (Spirochaetaceae); \*\*\**Borrelia*\*\*\*

*japonica* rpoB gene (Spirochaetaceae); \*\*\**Borrelia*\*\*\* *lusitaniae*

rpoB gene (Spirochaetaceae); \*\*\**Borrelia*\*\*\* *turicatae* rpoB gene

(Spirochaetaceae); \*\*\**Borrelia*\*\*\* *valaisiana* rpoB gene

(Spirochaetaceae)

ORGN Super Taxa

Enterobacteriaceae: Facultatively Anaerobic Gram-Negative Rods,

Eubacteria, Bacteria, Microorganisms; Spirochaetaceae: Spirochaetales,

Spirochetes, Eubacteria, Bacteria, Microorganisms

ORGN Organism Name

\*\*\**Borrelia*\*\*\* *afzelii* (Spirochaetaceae): pathogen, strain-IPer3,

strain-M7, strain-PKo-85, strain-VS461-T; \*\*\**Borrelia*\*\*\* *andersonii*

(Spirochaetaceae): pathogen, strain-21123; \*\*\**Borrelia*\*\*\* *bissettii*

(Spirochaetaceae): pathogen, strain-DN127-T; \*\*\**Borrelia*\*\*\*

*burgdorferi* (Spirochaetaceae): pathogen, strain-B31-T, strain-IP2;

\*\*\**Borrelia*\*\*\* \*\*\**garinii*\*\*\* (Spirochaetaceae): pathogen,

strain-G2, strain-G25, strain-HP13, strain- \*\*\*IP90\*\*\* , strain-PD89,

strain-Pbi, strain-Sika1, strain-Sika2; \*\*\**Borrelia*\*\*\* *hermsii*

(Spirochaetaceae): HS1-T, pathogen; \*\*\**Borrelia*\*\*\* *japonica*

(Spirochaetaceae): pathogen, strain-HO14-T; \*\*\**Borrelia*\*\*\*

*lusitaniae* (Spirochaetaceae): pathogen, strain-PotiB2-T;

\*\*\**Borrelia*\*\*\* *turicatae* (Spirochaetaceae): pathogen, strain-M2007;

\*\*\**Borrelia*\*\*\* *valaisiana* (Spirochaetaceae): pathogen,

strain-VS116-T; Escherichia coli (Enterobacteriaceae)

ORGN Organism Superterms

Bacteria; Eubacteria; Microorganisms

L15 ANSWER 15 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2000:388142 BIOSIS

DN PREV200000388142

TI Characteristics of the vls locus of \*\*\**Borrelia*\*\*\* \*\*\**garinii*\*\*\*

\*\*\*Ip90\*\*\* .

AU Wang, D. (1); Norris, S. J. (1)

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Microbiology Los Angeles, California, USA May 21-25, 2000 American Society  
for Microbiology  
. ISSN: 1060-2011.

DT Conference

LA English

SL English

TI Characteristics of the vls locus of \*\*\**Borrelia*\*\*\* \*\*\**garinii*\*\*\*

\*\*\*Ip90\*\*\* .

ORGN Super Taxa

Spirochaetaceae: Spirochaetales, Spirochetes, Eubacteria, Bacteria,  
Microorganisms  
ORGN Organism Name  
\*\*\**Borrelia*\*\*\* \*\*\**garinii*\*\*\* (Spirochaetaceae): pathogen,  
strain- \*\*\**Ip90*\*\*\* ; \*\*\**Borrelia*\*\*\* spp. (Spirochaetaceae):  
pathogen  
ORGN Organism Superterms  
Bacteria; Eubacteria; Microorganisms

L15 ANSWER 16 OF 21 USPATFULL  
AN 1998:162259 USPATFULL  
TI Decorin binding protein compositions and methods of use  
IN Guo, Betty, Houston, TX, United States  
Hook, Magnus, Houston, TX, United States  
PA The Texas A & M University System, College Station, TX, United States  
(U.S. corporation)  
PI US 5853987 19981229  
AI US 1996-589711 19960122 (8)  
RLI Continuation-in-part of Ser. No. US 1995-427023, filed on 24 Apr 1995,  
now abandoned  
DT Utility  
FS Granted

EXNAM Primary Examiner: Horlick, Kenneth R.; Assistant Examiner: Tung, Joyce

LREP Arnold, White & Durkee

CLMN Number of Claims: 68

ECL Exemplary Claim: 1

DRWN 25 Drawing Figure(s); 14 Drawing Page(s)

LN.CNT 4684

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\**Borrelia*\*\*\* *burgdorferi*, the etiological agent of Lyme disease, and DNA segments encoding dbp from related \*\*\**borrelbias*\*\*\* . Also disclosed are decorin binding protein compositions and methods of use. The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathological \*\*\**Borrelia*\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and anti-(decorin binding protein) antibodies will also be of use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\**Borrelia*\*\*\* colonization in an animal. These DNA segments and the peptides derived therefrom are contemplated for use in the preparation of vaccines and, also, for use as carrier proteins in vaccine formulations, and in the formulation of compositions for use in the prevention of Lyme disease.

AB Disclosed are the dbp gene and dbp-derived nucleic acid segments from \*\*\**Borrelia*\*\*\* *burgdorferi*, the etiological agent of Lyme disease, and DNA segments encoding dbp from related \*\*\**borrelbias*\*\*\* . Also disclosed are decorin binding protein compositions and methods of use. The DBP protein and antigenic epitopes derived therefrom are contemplated for use in the treatment of pathological \*\*\**Borrelia*\*\*\* infections, and in particular, for use in the prevention of bacterial adhesion to decorin. DNA segments encoding these proteins and. . . of use in various screening, diagnostic and therapeutic applications including active and passive immunization and methods for the prevention of \*\*\**Borrelia*\*\*\* colonization in an animal. These DNA segments and

the peptides derived therefrom are contemplated for use in the preparation of . .

SUMM . . . proteins derived from bacterial species. More particularly, the invention provides gene compositions encoding a decorin (Dcn) binding protein (DBP) from \*\*\*Borrelia\*\*\* burgdorferi and the corresponding peptide epitopes and protein sequences comprising native and synthetically-modified Dcn binding site domains. Various methods for. .

SUMM Lyme disease (Steere, 1989), or Lyme \*\*\*borreliosis\*\*\*, is transmitted by ticks, particularly of the genus *Ixodes*, and caused by spirochetes of the genus \*\*\*Borrelia\*\*\*. Lyme disease agents, that is \*\*\*borrelia\*\*\* isolated from humans or animals with clinical Lyme disease, are currently classified into at least three phylogenetic groups: *B. burgdorferi* sensu stricto, *B. \*\*\*garinii\*\*\**, and *B. afzelii*. Strains potentially representing other phylogenetic groups of Lyme disease agents as well, such as group 25015, have. .

SUMM . . . vitro-grown or tick-borne *B. burgdorferi*. Based largely on the protective efficacy of experimental OspA vaccines in rodent models of Lyme \*\*\*borreliosis\*\*\*, three monovalent OspA-based vaccines are currently in clinical trials. However, recent findings suggest that broad, sustained protection of humans may. .

SUMM c) OspA is serologically diverse, particularly among European and Asian *B. \*\*\*garinii\*\*\** and *B. afzelii* isolates. Reactivity with panels of OspA monoclonal antibodies (mAbs), and DNA sequence analysis has shown that as. .

SUMM . . . and Bockenstedt, 1993). OspA is expressed by *B. burgdorferi* within ticks (Barbour et al., 1983), but detection of OspA on \*\*\*borrelia\*\*\* in tissue early after infection is difficult. Passive immunization of mice with OspA antibody (Schaible et al., 1990), or immunization. .

SUMM . . . vivo only at later stages when the infection becomes disseminated. This would be explained by down-regulation of OspA expression by \*\*\*borrelia\*\*\* shortly after initiation of feeding by the tick.

SUMM Modulation of \*\*\*borrelia\*\*\* antigen expression within feeding ticks has recently been reported for OspC; initially low in resting ticks, OspC levels increase on. .

SUMM . . . to pre-exist at high levels in human or animal hosts prior to the tick bite to be effective against OspA-expressing \*\*\*borrelia\*\*\* in the tick, and may receive little or no boosting upon delivery of the spirochetes into the skin within the. .

SUMM . . . the gut of the infecting tick, before inoculation of the pathogen." Consistent with this hypothesis it has been shown that anti- \*\*\*borrelia\*\*\* serum can protect mice from infection by tick bite if administered within two days after initiation of feeding by \*\*\*borrelia\*\*\* -infected ticks, but not when passively administered at later times (Shih et al., 1995). The antibody levels in response to recombinant. .

SUMM . . . the host cell ECM component, Dcn. Also disclosed are methods for active and passive immunization against *B. burgdorferi* and related \*\*\*borrelia\*\*\* including *B. afzelii* and *B. \*\*\*garinii\*\*\** using novel native and site-specifically-altered DBP compositions and DBP-derived epitopic peptides from *B. burgdorferi*, *B. afzelii* and *B. \*\*\*garinii\*\*\**. Particular aspects of the invention relate to novel nucleic acid segments encoding these peptides and epitopes, and methods

for the. . .

SUMM SEQ ID NO:1 comprises the complete nucleotide sequence of a 2.5 kb insert of \*\*\*borrelia\*\*\* genomic DNA cloned in the pBlueScript.TM. vector. This recombinant clone, designated BG26:pB/2.5(5), has been deposited with the American Type Culture. . .

SUMM . . . DBPs. Strain variants are those nucleic acid compositions and polypeptide compositions expressed by various strains of *B. burgdorferi* and related \*\*\*borrelia\*\*\* including *B. afzelii* and *B.*

\*\*\*garinii\*\*\* which specifically encode DBPs. These DBPs also bind Dcn and related proteoglycans and share similarity of structure and function with. . .

SUMM . . . alternatively by the demonstrating the ability of the strain-variant DBP to lessen or prevent adherence of *B. burgdorferi* and related \*\*\*borrelia\*\*\* including *B. afzelii* and *B. \*\*\*garinii\*\*\** to Dcn.

SUMM . . . be used, so long as the coding segment employed encodes a protein or peptide of interest (e.g., a DBP from \*\*\*Borrelia\*\*\*, and particularly a DBP from *B. burgdorferi*, *B. afzelii*, or *B.*

\*\*\*garinii\*\*\*, and does not include any coding or regulatory sequences that would have an adverse effect on cells. Therefore, it will. . .

SUMM . . . it will direct the expression and production of the protein or peptide epitope of interest (e. g., a DBP from \*\*\*Borrelia\*\*\* and in particular, from *B. burgdorferi*, *B. afzelii*, *B. \*\*\*garinii\*\*\**, or *B. japonica*) when incorporated into a host cell. In a recombinant expression vector, the coding portion of the DNA. . .

SUMM . . . antibodies for diagnostic and therapeutic methods relating to the detection and treatment of infections caused by *B. burgdorferi* and related \*\*\*borrelia\*\*\* including *B. afzelii* and *B. \*\*\*garinii\*\*\**

SUMM . . . The nucleic acid sequences encoding DBP are useful as diagnostic probes to detect the presence of *B. burgdorferi*, and related \*\*\*borrelia\*\*\* including *B. afzelii* and *B. \*\*\*garinii\*\*\** in a test sample, using conventional techniques. In one such method of diagnosing \*\*\*Borrelia\*\*\* infection, dbp nucleic acid segments may be used in Southern hybridization analyses or Northern hybridization analyses to detect the presence. . .

SUMM . . . serum concentration of DBP-reactive antibodies that is at least twice that required for inhibition of in vitro growth of endemic \*\*\*borrelia\*\*\* strains. It is contemplated that the duration of dosing maintaining anti-DBP levels at these inhibitory antibody concentrations would be for. . .

SUMM . . . length will often be preferred. The antigenic proteins or peptides may also be combined with other agents, such as other \*\*\*borrelia\*\*\* peptide or nucleic acid compositions, if desired.

SUMM . . . methods for the stimulation of an immune response include vaccination regimens designed to prevent or lessen significant infections caused by \*\*\*borrelia\*\*\* or other bacteria expressing a DBP, and treatment regimens that may lessen the severity or duration of any infection, it. . . treatment methods may be used particularly for the treatment of infections caused by pathogens such as *B. burgdorferi*, *B. afzelii*, *B. \*\*\*garinii\*\*\**, related \*\*\*borrelia\*\*\* species, and other bacteria which express DBPs and adhere to Dcn.

SUMM Immunoformulations of this invention, whether intended for vaccination, treatment, or for the generation of antibodies useful in the detection of \*\*\*borrelia\*\*\* and in particular *B. burgdorferi*, the prevention

of bacterial adhesion, or in the case of bacterial colonization, promotion of bacterial. . .

SUMM . . . in the immunodetection of compounds, present within clinical samples, that are indicative of Lyme disease or related infections caused by \*\*\*borrelia\*\*\*, and in particular *B. burgdorferi*. The kits may also be used in antigen or antibody purification, as appropriate.

SUMM . . . even perhaps urine samples may be employed. This allows for the diagnosis of Lyme disease and related infections caused by \*\*\*borrelia\*\*\*, and in particular, *B. burgdorferi*. Furthermore, it is contemplated that such embodiments may have application to non-clinical samples, such as. . .

SUMM . . . and peptides, in particular those DBP proteins isolated from prokaryotic sources, and particularly bacteria. DNA segments isolated from species of \*\*\**Borrelia*\*\*\* and related bacteria which are shown to bind Dcn are particularly preferred for use in the methods disclosed herein. Such. . .

SUMM . . . particularly contemplated to be useful in the production of Anti-DBP antibodies for use in passive immunization methods for prevention of \*\*\*borrelial\*\*\* adhesion to Dcn, and treatment of infections due to \*\*\**Borrelia*\*\*\* invasion, and particularly invasion by *B. burgdorferi*.

SUMM . . . vaccine compositions useful in the prevention of Lyme disease and antibody compositions useful in the prevention of Dcn binding to \*\*\**Borrelia*\*\*\*.

SUMM . . . bacterial cells. These aspects provide methods and compositions for producing bacterial colonization of an animal host with attenuated, or avirulent \*\*\**Borrelia*\*\*\* expressing cell surface DBP epitopes.

SUMM . . . with an antibody composition disclosed herein, and detecting the formation of immune complexes. In preferred embodiments, the bacterium is a \*\*\*borrelia\*\*\*, and most preferably, a *B. burgdorferi*, *B. afzelii*, or *B. garinii* strain.

SUMM . . . include pharmaceutically-acceptable formulations of either the antibodies or peptide antigens disclosed herein. Such kits are useful in the detection of \*\*\*borrelia\*\*\* in clinical samples, and also useful for inhibiting or promoting the binding of \*\*\*borrelia\*\*\* to the ECM component, Dcn. In preferred embodiments, the bacteria detected using such kits include \*\*\*borrelia\*\*\*, and in particular, *B. burgdorferi*, *B. afzelii*, *B. garinii*, or related species.

SUMM Other aspects of the invention include methods of inhibiting bacterial colonization, and particularly colonization by \*\*\*borrelia\*\*\*, in an animal by administering to the animal an antibody of the present invention which prevents or significantly reduces the. . . the antibody composition may be prophylactically prior to and/or following diagnosis of Lyme disease or other multisystemic disorders caused by \*\*\**Borrelia*\*\*\* which may involve the skin, joints, heart, and central nervous system. The administration may also be made in passive immunization. . .

SUMM . . . other Gram-negative hosts including various *Pseudomonas* species may be used in the recombinant expression of the genetic constructs disclosed herein. \*\*\**Borrelia*\*\*\* themselves may be used to express these constructs, and in particular, *B. burgdorferi*, *B. afzelii*, *B. japonica* and *B. garinii*.

DRWD . . . tissue samples (bladder, FIG. 12A; ear, FIG. 12B; and joint, FIG. 12C) were placed in BSKII medium and evidence of \*\*\*borrelial\*\*\*

outgrowth from these tissues was assessed microscopically after 2 wk of in vitro culture at 34.degree. C.; 10-20 high power fields of samples of the cultures were examined before judging tissues to be uninfected. The number of visible \*\*\*borrelia\*\*\* per microscopic field in organ cultures from each mouse are shown. Bladder tissue is a very sensitive indicator of \*\*\*borrelial\*\*\* infection, while joint and skin are also sources of \*\*\*borrelial\*\*\* infection, thus all three tissue samples were routinely assayed. Complete protection was judged when no spirochetes were recoverable from all three tissue sites. Partial or intermediate detection was determined when no \*\*\*borrelias\*\*\* were detectable in joint and skin samples, but a few remaining bacteria were present in bladder tissue.

DRWD FIG. 13. Membrane localization of candidate \*\*\*borrelia\*\*\* vaccine antigens. *B. burgdorferi* B31 total membranes were separated into inner- (IM, lane 2) and outer-membranes (OM, lane 4) using. . . by others (Bledsoe et al., 1994). By detergent phase portioning DBP appears to be amphiphilic as are OspA and other \*\*\*borrelia\*\*\* membrane lipoproteins (Brandt et al., 1990).

DRWD . . . Five combinations of these oligonucleotides were used as primer pairs for PCR.TM. amplification studies with genomic DNA templates from various \*\*\*borrelia\*\*\* strains. The sizes, in base pairs, of the dbp gene segments expected, based on the strain 297 sequence, from these. . .

DETD . . . is anticipated to be especially effective in treatment regimens for Lyme disease, and as a cost-effective prophylaxis for prevention of \*\*\*borrelial\*\*\* infections.

DETD . . . limitations of the prior art, particularly with respect to OspA and other antigens previously investigated as antigens for development of \*\*\*borrelia\*\*\* vaccines. Indeed, vaccine compositions comprising DBPs are likely to be superior to those previously available containing OspA alone.

DETD . . . of OspA as antibodies reactive with DBP derived from *B. burgdorferi* sensu stricto are also growth-inhibitory to strains of *B. garinii* and *B. afzelii*.

DETD 4.2.5. Anti-DBP Antibodies Eliminate \*\*\*Borrelia\*\*\* From Infected Animals

DETD 4.2.6 dbp Nucleic Acid Segments Useful in Identifying \*\*\*Borrelial\*\*\* Isolates

DETD . . . and isolate molecular clones of alleles of this gene present in different phylogenetic groups of Lyme disease spirochetes including *B. garinii* and *B. afzelii* by utilization of such techniques as PCR.TM..

DETD . . . kDa. However, due to the copurification of the DBP with other *B. burgdorferi* proteins, complete purification of native DBP from \*\*\*borrelia\*\*\* in pure form has not been achieved.

DETD . . . antibodies to gene products encoded by such nucleic acid segments, or in the production of diagnostic and treatment protocols for \*\*\*borrelia\*\*\* infection, and in particular, infection with *B. burgdorferi*, *B. afzelii*, or *B. garinii*, and those infections leading to Lyme disease. Any and all such combinations are intended to fall within the scope of. . .

DETD . . . from which the DBP composition may be applied to a tissue site, skin lesion, wound area, or other site of \*\*\*borrelial\*\*\* infection. However, the single container means may contain a dry, or lyophilized, mixture of a DBP composition, which may or. . .

DETD . . . analyze the distribution of bacteria expressing DBPs during cellular infection, for example, to determine the cellular or tissue-specific distribution of \*\*\*borrelia\*\*\* under different physiological conditions. A particularly useful application of such antibodies is in purifying native or recombinant DBPs, for example, . . .

DETD 4.14 DBP Compositions for Treating \*\*\*Borrelia\*\*\* Infections  
DETD . . . quantities. The selected antigens, and variants thereof, are proposed to have significant utility in diagnosing and treating infections caused by \*\*\*borrelia\*\*\* and in particular, *B. burgdorferi*, *B. garinii* and *B. afzelii*. For example, it is proposed that rDBPs, peptide variants thereof, and/or antibodies against such rDBPs may also be used in immunoassays to detect \*\*\*borrelia\*\*\* or as vaccines or immunotherapeutics to treat \*\*\*borrelia\*\*\* infections, and to prevent bacterial adhesion to ECM components such as Dcn in the same manner as native DBP compositions.

DETD The peptides provided by this invention are ideal targets for use as vaccines or immunoreagents for the treatment of various \*\*\*borrelia\*\*\*-related diseases, and in particular, those caused by species which contain DBP and DBP-encoding genes, and hence those which express either. . .

DETD The \*\*\*Borrelia\*\*\* binding site on the Dcn molecule has not been identified. Presumably, Dcn binds both collagen and \*\*\*borrelia\*\*\* at once, with the two interactions involving different sites on the proteoglycan. The requirement of intact Dcn adhesin on the. . .

DETD . . . adhesive function of DBP, and its role as a target for growth-inhibitory antibodies, imply that DBP is localized to the \*\*\*borrelia\*\*\* outer membrane. To provide additional biochemical support for this *B. burgdorferi* B3 total membranes were separated into inner and outer. . . (Bledsoe et al., 1994). By detergent phase partitioning DBP appears to be amphiphilic (FIG. 13) as are OspA and other \*\*\*borrelia\*\*\* membrane lipoproteins (Brandt et al., 1990). To confirm the presence of lipid on these proteins *B. burgdorferi* B31 was metabolically. . .

DETD Identification of DBPs in \*\*\*borrelia\*\*\* Isolates

DETD One aspect of the present invention, is the identification of \*\*\*borrelia\*\*\* using the DBP compositions disclosed herein as diagnostic indicators of \*\*\*borrelia\*\*\* infection. As shown in Table 2, an assay of DBP in \*\*\*borrelia\*\*\* using Western hybridization analyses, it was possible to identify the presence of DBPs in at least 13 strains of *B. burgdorferi*, 5 strains of *B. garinii*, and at least three strains of *B. afzelii*. These methods represent important diagnostic tools for the identification of bacteria in. . .

DETD TABLE 2

Assay of DBP in \*\*\*borrelia\*\*\* By Western Blot

Strain	Origin	DBP	Source
--------	--------	-----	--------

B burgdorferi			
N40	tick	+	S. Norris
N40	tick	+	S. Norris
Sh2	tick	+	S. Norris
Sh2	tick. . . skin	+	J. Leong
LP7	skin	+	J. Leong

G39/40	tick	+	J. Leong	
297	CSF	+	R. Isaacs	
25015	tick	+	M. Hanson	
B. ***garinii***				
PBi	CSF	+	J. Leong	
PBi	CSF	+	J. Leong	
G2	CSF	+	J. Leong	
PBr	CSF	+	M. Hanson	
B4-91	CSF	+	M. Hanson	
***Ip90***		tick	+	M. Hanson
B afzelii				
PKo	skin	+	M. Hanson	
ACA1	skin	+	M. Hanson	
PGau	skin	+	M. Hanson	

DETD 5.6 DBP Compositions Block Adherence of \*\*\*borrelia\*\*\* to Decorin

DETD Inhibitory activity of anti-rDBP serum towards in vitro growth of

\*\*\*Borrelia\*\*\* strains of diverse origin

DETD Two other \*\*\*borrelia\*\*\* proteins, OspA and OspB, believed to be surface-exposed have been shown to be targets for bacterial killing by specific antibodies. . . protein's exposure at the surface of a cell.

Rabbit antisera were serially diluted in 96 well plates, 10.sup.5 mid-log phase \*\*\*borrelia\*\*\* in BSK II medium were added per well, the mixture was incubated for three days, and cell viability (motility) was. . . anti-rOspA serum, used as a positive control, to about 1:50,000 for B. burgdorferi sensu stricto strains including the homologous strain 297. \*\*\*Borrelia\*\*\* incubated in serum raised against a Streptococcus pneumoniae protein, PspA, were fully motile. Significantly, serum raised against DBP from B.. . .

DETD . . . of the donors can be purified and systemically administered to a target population. Those individuals at high risk for developing \*\*\*borrelia\*\*\* infections include, but are limited to, patients in intensive care units, immunocompromised patients, surgery patients, children, and persons in areas. . . infestations such as the northeastern, midwestern, and western pacific United States. Two particular references which describe those at risk from \*\*\*borrelioses\*\*\* include Steere, 1994 and a report by the Centers for Disease Control, 1994.

DETD At two weeks post-challenge tissue samples (bladder, heart, synovial fluid) are placed in BSKII medium and evidence of \*\*\*borrelial\*\*\* outgrowth from these tissues is assessed microscopically after 2 and 3 wk of in vitro culture. Protection is judged to. . .

DETD . . . that accessibility of DBP to antibodies is not an artifact of in vitro manipulation is to demonstrate passive protection from \*\*\*borrelia\*\*\* challenge with these antibodies. Even though common strains of inbred mice (such as C3H/HeJ, C3H/HeN, and Balb/cByJ; Barthold et al., 1993) may differ in the severity of disease elicited by \*\*\*borrelia\*\*\*, their sensitivities to infectious \*\*\*borrelia\*\*\* strains is more uniform.

DETD . . . (Sadziene et al., 1993) (Table 7). Rabbit antisera were serially diluted in 96-well plates in 0.1 ml BSKII medium, 10.sup.5 \*\*\*borrelia\*\*\* in the mid-log phase of growth in 0.1 ml BSKII medium were added per well, the mixture was incubated for. . . was strongly inhibitory to growth of all three B. burgdorferi sensu stricto strains, as well as several of the B. \*\*\*garinii\*\*\* and B. afzelii strains.

One *B. afzelii* strain, PGau, was slightly inhibited at a 1:50 serum dilution. Strain 25015 was . . . into at least four OspA serogroups, and have diverse geographic origins. Serum against an irrelevant antigen, PspA, was not inhibitory. \*\*\**Borrelia*\*\*\* strains were obtained from the laboratories of Drs. Steve Norris, John Leong, Alan Barbour, Robert Lane, Robin Isaacs, David Dorward, . . .

DETD Identification of candidate dbp alleles from *B. burgdorferi*, *B. afzelii*, and *B. garinii* was accomplished using oligonucleotides diagrammed in FIG. 14 as primers for PCRTM amplifications of dbp gene fragments from \*\*\**borrelia*\*\*\* strains representing the three major phylogenetic groups of Lyme disease spirochetes. Portions of the PCR.TM. amplification reactions were electrophoresed on. . .

DETD . . . to infection. This suggests that an infection-induced memory response to OspA will be of little or no benefit. However, other \*\*\**borrelia*\*\*\* surface proteins required for growth and persistence in vivo may not suffer this limitation as vaccine immunogens. Many bacterial pathogens including \*\*\**borrelia*\*\*\* initiate infection following adhesion to specific macromolecules of the host target tissue. These adhesins are exposed at the bacterial surface.. . .

DETD . . . favorable pharmacokinetics. The studies measured only infection rather than disease, however, antibody levels which are not sufficient to eliminate all \*\*\**borrelia*\*\*\* may in fact be sufficient to prevent disease pathologies.

DETD Isolation of Nucleic Acid Sequences Encoding DBPs from *B. burgdorferi*, *B. afzelii*, and *B. garinii*

DETD Oligonucleotides diagrammed in FIG. 14 were used as primers for PCR.TM. amplifications of dbp gene fragments from \*\*\**borrelia*\*\*\* strains representing the three major phylogenetic groups of Lyme disease spirochetes. Primers derived from the dbp gene of strain 297. . .

DETD TABLE 6

In vitro Growth Inhibitory Activity of Rabbit Anti-rDB.sub.297 Serum Against Diverse \*\*\**Borrelia*\*\*\* Strains

Strain	Origin	Serogroup	Growth Inhibition by	
			Anti-rDBP.sub.297	
			OspA	Growth
		sup.b		
		Inhibition		
		Titer		

<i>B. burgdorferi</i>					
B31	Tick, USA	1	+++	5,120	
297	CSF, USA	1	+++. . .	1	+++ 5,120
<i>B. afzelii</i>					
PKo	Skin, Germany	2	+++	12,800	
PGau	Skin, Germany	2	+/-	1:50.sup.c	
ACA I	Skin, Sweden	2	-	<1:50.sup.d	
<i>B. garinii</i>					
PBr	CSF, Germany	3	+++	12,800	
PBi	CSF, Germany	4	++	800	

B4 91 Skin, Norway  
 ? - <100.sup.d  
 G2.22 CSF, Germany  
 ? - <50.sup.d  
 \*\*\*Ip90\*\*\* Tick, Russia  
 x - <50.sup.d  
 25015 Group.sup.a  
 25015 Tick, USA ? +/- .about.1:25.sup.c

.sup.a phylogenetically distinct from *B. burgdorferi* sensu stricto:  
 Casjens. . .

DETD TABLE 7

Effect of Post-Challenge Passive Administration of  
 Antisera on \*\*\*Borrelia\*\*\* Infection in C3H/HeJ Mice  
 Number of Mice Infected at Each  
 Day of Serum Administration

Antiserum	0	2	4	7	10
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DBP 0/3. . .

DETD TABLE 8

Amplification of a DBP Allele from Various \*\*\*Borrelia\*\*\* Species

Expected	DBP	DBP	DBP	DBP	DBP
Full Length					
Truncate					
Pair 1					
Pair 2					
Pair 3					

Species Strain

564 bp					
448.	.	.	+	+	+
5H2	+	+	+	+	+

*B. afzelli*

ACA-1					
+	-	-	+		

pGAU

+	+	-			
---	---	---	--	--	--

*B. garinii*  
\*\*\*IP90\*\*\*

+	+	-			
---	---	---	--	--	--

B491

+	-	-	-	-	-
pBi	-	-	-	-	-

DETD Barthold et al., "Animal Model: Chronic Lyme \*\*\*borreliosis\*\*\* in the Laboratory Mouse," Am. J. Pathol., 143:959-971, 1993.

DETD Barthold et al., "Kinetics of \*\*\*Borrelia\*\*\* burgdorferi Dissemination and Evolution of Disease After Intradermal Inoculation of Mice," Am. J. Pathol., 139:263-273, 1991.

DETD Barthold et al., "Lyme \*\*\*borreliosis\*\*\* in the Laboratory Mouse," In: Lyme Disease: Molecular and Immunology Approaches, S. E. Schutzer (ed.), Cold Spring Harbor Press, Plainview, . . .

DETD Coburn et al., "Integrin .alpha..sub.IIb .beta..sub.3 Mediates Binding of the Lyme Disease Agent \*\*\*Borrelia\*\*\* burgdorferi to Human Platelets," Proc. Natl. Acad. Sci. USA, 90:7059-7063, 1993.

DETD Duray, "Target Organs of \*\*\*Borrelia\*\*\* burgdorferi Infections: Functional Responses and Histology," In: Lyme Disease: Molecular and Immunologic Approaches, S. E. Schutzer (ed.), Cold Spring Harbor. . .

DETD Haupl et al., "Persistence of \*\*\*Borrelia\*\*\* burgdorferi in Ligamentous Tissue From a Patient With Chronic Lyme \*\*\*borreliosis\*\*\*," Arthritis Rheum., 36:1621-1626, 1993.

DETD Isaacs, " \*\*\*Borrelia\*\*\* burgdorferi Bind to Epithelial Cell Proteoglycans," J. Clin. Invest., 93:809-819, 1994.

DETD Zimmer et al., "Lyme Carditis in Immunodeficient Mice During Experimental Infection of \*\*\*Borrelia\*\*\* burgdorferi," Virchows Arch. A Pathol. Anat., 417:129-135, 1990.

CLM What is claimed is:

9. The isolated nucleic acid of claim 1, further defined as encoding a B. burgdorferi, B. \*\*\*garinii\*\*\* , or B. afzelii decorin binding protein.

16. The isolated nucleic acid of claim 15, wherein said isolated nucleic acid encodes a \*\*\*Borrelia\*\*\* decorin binding protein.

17. The isolated nucleic acid of claim 16, wherein said isolated nucleic acid encodes a B. burgdorferi, B. \*\*\*garinii\*\*\* , or B. afzelii decorin binding protein.

51. The recombinant host cell of claim 50, wherein said bacterial cell is an E. coli, B. burgdorferi, B. \*\*\*garinii\*\*\* , or B. afzelii cell.

63. The method of claim 62, wherein said isolated nucleic acid encodes a \*\*\*Borrelia\*\*\* decorin binding protein.

64. The method of claim 63, wherein said isolated nucleic acid encodes a B. burgdorferi, B. \*\*\*garinii\*\*\* , or a B. afzelii decorin binding protein.

L15 ANSWER 17 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

6

AN 1997:155733 BIOSIS

DN PREV199799454936

TI Consensus sequence on the genes encoding the major outer surface proteins (OspA and OspB) of \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* isolate.

AU Jianhui, Wang (1); Masuzawa, Toshiyuki; Komikado, Tetsuro; Yanagihara, Yasutake

CS (1) Dep. Microbiol., Sch. Pharmaceutical Sci., Univ. Shizuoka, 52-1 Yada, Shizuoka, Shizuoka 422 Japan

SO Microbiology and Immunology, (1997) Vol. 41, No. 2, pp. 83-91.

ISSN: 0385-5600.

DT Article

LA English

AB Japanese Lyme \*\*\*borrelia\*\*\* classified as ribotype IV is predominant among isolates derived from clinical specimens, reservoir rodents and Ixodes persulcatus ticks, and has been characterized as \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\* . These B. \*\*\*garinii\*\*\* isolates have antigenic and

genetic features apparently different from North American, European and other Asian isolates, especially in major outer surface proteins A (OspA) and B (OspB). In this study, we cloned and sequenced the genes encoding OspA and OspB from *B. garinii* strain FujiP2 (ribotype IV strain) isolated from *Ixodes persulcatus* in Shizuoka, Japan. A sequence analysis revealed significant differences to the previously published sequences of ospA and ospB of *B. burgdorferi* sensu lato. The open reading frames of ospA and ospB consist of 822 and 888 nucleotides corresponding to the proteins of 273 and 295 amino acids, with molecular weights of 29,643 and 31,786 daltons, respectively. The most interesting finding is that the two osp genes share a consensus 282 bp sequence in their carboxy-terminal portions and that the ospB gene is flanked by a 282 bp-long direct repeat sequence. The deduced amino-acid (aa) sequences of OspA and OspB of strain FujiP2 showed 60.1% homology, and have overall similarities of 70.5%, 70.3% and 75.6% to OspAB proteins of *B. burgdorferi* sensu stricto strain B31, *Borrelia afzelii* strain ACA1 and *Borrelia garinii* strain 1p90, respectively.

TI Consensus sequence on the genes encoding the major outer surface proteins (OspA and OspB) of *Borrelia garinii* isolate.

AB Japanese Lyme borreliosis classified as ribotype IV is predominant among isolates derived from clinical specimens, reservoir rodents and *Ixodes persulcatus* ticks, and has been characterized as *Borrelia garinii*. These *B. garinii* isolates have antigenic and genetic features apparently different from North American, European and other Asian isolates, especially in major outer A (OspA) and B (OspB). In this study, we cloned and sequenced the genes encoding OspA and OspB from *B. garinii* strain FujiP2 (ribotype IV strain) isolated from *Ixodes persulcatus* in Shizuoka, Japan. A sequence analysis revealed significant differences to the . . . homology, and have overall similarities of 70.5%, 70.3% and 75.6% to OspAB proteins of *B. burgdorferi* sensu stricto strain B31, *Borrelia afzelii* strain ACA1 and *Borrelia garinii* strain 1p90, respectively.

IT . . .  
GENE SEQUENCE; HOST; INFECTION; LYME DISEASE; MOLECULAR GENETICS; OUTER SURFACE PROTEIN A; OUTER SURFACE PROTEIN B; PATHOGEN; STRAIN-ACA1; STRAIN-B31; STRAIN-FUJIP2; STRAIN- 1p90 ; U49190

ORGN . . .

Unspecified: Rodentia, Mammalia, Vertebrata, Chordata, Animalia;  
*Spirochaetaceae*: Eubacteria, Bacteria

ORGN Organism Name

human (Hominidae); rodent (Rodentia - Unspecified); tick (Acarina);  
*Borrelia afzelii* (*Spirochaetaceae*); *Borrelia garinii*  
*burgdorferi* (*Spirochaetaceae*); *Borrelia garinii*  
(*Spirochaetaceae*); *Ixodes persulcatus* (Acarina); Rodentia (Rodentia - Unspecified)

ORGN Organism Superterms

animals; arthropods; bacteria; chelicerates; chordates; eubacteria;  
humans; invertebrates; mammals; . . .

L15 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2002 ACS

AN 1996:121191 CAPLUS

DN 124:167520

TI Cloning and expression of gene for 66 kilodalton antigen from *Borrelia* and vaccines for lyme disease

IN Bergstroem, Sven; Barbour, Alan George

PA Symbicom AB, Swed.

SO PCT Int. Appl., 119 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 7

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9535379	A1	19951228	WO 1995-US7665	19950619
	W:	AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT		
	RW:	KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG		
US 6054296	A	20000425	US 1994-262220	19940620
AU 9528632	A1	19960115	AU 1995-28632	19950619
AU 686407	B2	19980205		
EP 766739	A1	19970409	EP 1995-923924	19950619
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE		
US 6204018	B1	20010320	US 1997-750494	19970612
PRAI US 1994-262220	A	19940620		
DK 1988-5902	A	19881024		
US 1989-422881	B1	19891018		
US 1992-924798	B1	19920806		
US 1993-79601	A2	19930622		
WO 1995-US7665	W	19950619		
AB	Nucleic acid fragments are disclosed which encode a polypeptide antigen reactive with antisera from rabbits immunized with a 66 kDa protein from ***Borrelia*** ***garinii*** ***IP90*** . The presence of nucleic acid fragments encoding such a polypeptide antigen as well as the presence of the polypeptide antigen have been demonstrated in three strains of B. burgdorferi sensu lato, but are substantially absent from at least 95% of randomly selected B. hermsii, B. crocidurae, B. anserina, and B. hispanica. The encoded polypeptide is surface exposed on the bacterial surface, it is highly conserved, and is thus potentially useful as a vaccine agent and as a diagnostic agent in the diagnosis of infections with B. burgdorferi as are the characteristic nucleic acid fragments of the invention. Also disclosed are methods of producing the polypeptide antigen according to the invention as are antibodies directed against the antigen.			
TI	Cloning and expression of gene for 66 kilodalton antigen from ***Borrelia*** and vaccines for lyme disease			
AB	Nucleic acid fragments are disclosed which encode a polypeptide antigen reactive with antisera from rabbits immunized with a 66 kDa protein from ***Borrelia*** ***garinii*** ***IP90*** . The presence of nucleic acid fragments encoding such a polypeptide antigen as well as the presence of the polypeptide antigen have been demonstrated in three strains of B. burgdorferi sensu lato, but are substantially absent from at least 95% of randomly selected B. hermsii, B. crocidurae, B. anserina, and B. hispanica. The encoded polypeptide is surface exposed on the bacterial surface, it is highly conserved, and is thus potentially useful as a vaccine agent and as a diagnostic agent in the diagnosis of infections with B. burgdorferi as are the characteristic nucleic acid fragments of			

the invention. Also disclosed are methods of producing the polypeptide antigen according to the invention as are antibodies directed against the antigen.

ST sequence 66 kilodalton antigen gene \*\*\*Borrelia\*\*\* ; vaccine lyme disease recombinant \*\*\*Borrelia\*\*\* antigen

IT Antigens

RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(66 kilodalton; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Lipoproteins

RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(E. coli outer membrane, fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Proteins, specific or class

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(PC, combination vaccine contg.; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Peptides, biological studies

RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(ZZ, fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Antibodies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(anti-66 kilodalton antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT \*\*\*Borrelia\*\*\* afzelii  
\*\*\*Borrelia\*\*\* burgdorferi  
\*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\*

Lyme arthritis

Vaccines

(cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Pilins

RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Proteins, specific or class

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(gene ospD, combination vaccine contg.; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Microorganism

(non-pathogenic, recombinant, as live vaccine; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Deoxyribonucleic acid sequences

(of 66 kilodalton antigen genes of \*\*\*Borrelia\*\*\* burgdorferi, B. afzelii, and B. \*\*\*garinii\*\*\* )

IT Protein sequences  
(of 66 kilodalton antigens of \*\*\*Borrelia\*\*\* burgdorferi, B. afzelii, and B. \*\*\*garinii\*\*\* )

IT Proteins, specific or class  
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(A, fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Lymphocyte  
(B-cell, epitope, fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Proteins, specific or class  
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(G, fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Proteins, specific or class  
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(MBP (maltose-binding protein), fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Proteins, specific or class  
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(NS1 (nonstructural, 1), of influenza virus, fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Lymphocyte  
(T-cell, epitope, fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Lipoproteins  
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(gene ospA, of B. burgdorferi, fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Lipoproteins  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(gene ospB, combination vaccine contg.; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Pilins  
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(gene papA, fusion products with 66 kDa antigen; cloning and expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT Antigens

RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL  
 (Biological study); PREP (Preparation); USES (Uses)  
 (hepatitis B core, fusion products with 66 kDa antigen; cloning and  
 expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\*  
 and vaccines for lyme disease)

IT Antigens  
 RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL  
 (Biological study); PREP (Preparation); USES (Uses)  
 (hepatitis B surface, fusion products with 66 kDa antigen; cloning and  
 expression of gene for 66 kilodalton antigen from \*\*\*Borrelia\*\*\*  
 and vaccines for lyme disease)

IT Antibodies  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (monoclonal, anti-66 kilodalton antigen; cloning and expression of gene  
 for 66 kilodalton antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme  
 disease)

IT 170214-03-6 170214-04-7 170214-05-8 173833-86-8  
 RL: PRP (Properties)  
 (amino acid sequence; cloning and expression of gene for 66 kilodalton  
 antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT 9031-11-2DP, .beta.-Galactosidase, fusion products with 66 kDa antigen  
 26062-48-6DP, Polyhistidine, fusion products with 66 kDa antigen  
 26854-81-9DP, Polyhistidine, fusion products with 66 kDa antigen  
 50812-37-8DP, Glutathione S-transferase, fusion products with 66 kDa  
 antigen  
 RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL  
 (Biological study); PREP (Preparation); USES (Uses)  
 (cloning and expression of gene for 66 kilodalton antigen from  
 \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

IT 166847-44-5 166847-46-7 173764-03-9 173764-04-0  
 RL: PRP (Properties)  
 (nucleotide sequence; cloning and expression of gene for 66 kilodalton  
 antigen from \*\*\*Borrelia\*\*\* and vaccines for lyme disease)

L15 ANSWER 19 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

7

AN 1995:268372 BIOSIS  
 DN PREV199598282672  
 TI Analyses of mammalian sera in enzyme-linked immunosorbent assays with  
 different strains of \*\*\*Borrelia\*\*\* burgdorferi sensu lato.  
 AU Magnarelli, Louis A. (1); Anderson, John F. (1); Johnson, Russell C.  
 CS (1) Dep. Entomol., Conn. Agric. Exp. Stn., P.O. Box 1106, New Haven, CT  
 06504 USA  
 SO Journal of Wildlife Diseases, (1995) Vol. 31, No. 2, pp. 159-165.  
 ISSN: 0090-3558.  
 DT Article  
 LA English  
 AB Blood samples were collected from cottontail rabbits (*Sylvilagus*  
*floridanus*), raccoons (*Procyon lotor*), white-footed mice (*Peromyscus*  
*leucopus*), and white-tailed deer (*Odocoileus virginianus*) between 1977 and  
 1991 in southern Connecticut and New York State (USA) and were tested for  
 antibodies against eight strains of \*\*\*Borrelia\*\*\* burgdorferi sensu  
 lato in enzyme-linked immunosorbent assays. Among these spirochetes were  
 six strains of *B. burgdorferi* sensu stricto, one strain of *B.*  
 \*\*\*garinii\*\*\* (= \*\*\*IP90\*\*\* ) and a strain (IPF) in group VS461. Sera

from each study group reacted positively to all strains having origins in North America and Eurasia. Assay sensitivities normally ranged between 85% and 100% for all study groups. The lowest sensitivity (66%) was noted when mouse sera were tested with B. *\*\*\*garinii\*\*\**, an isolate from *Ixodes persulratus* in the former Soviet Union. Differences in serum reactivity to various strains were noted for all study groups, but because of multiple shared antigens among the closely related spirochetes tested, the selection of a particular North American strain of *B. burgdorferi sensu stricto* did not appear to be a critical factor for optimal assay performance. Locally obtained strains of this bacterium are preferred as coating antigens for serologic testing because of their availability.

TI Analyses of mammalian sera in enzyme-linked immunosorbent assays with different strains of *\*\*\*Borrelia\*\*\* burgdorferi sensu lato*.

AB . . . 1977 and 1991 in southern Connecticut and New York State (USA) and were tested for antibodies against eight strains of *\*\*\*Borrelia\*\*\* burgdorferi sensu lato* in enzyme-linked immunosorbent assays. Among these spirochetes were six strains of *B. burgdorferi sensu stricto*, one strain of *B. \*\*\*garinii\*\*\** (= *\*\*\*IP90\*\*\**) and a strain (IPF) in group VS461. Sera from each study group reacted positively to all strains having origins in . . . 85% and 100% for all study groups. The lowest sensitivity (66%) was noted when mouse sera were tested with *B. \*\*\*garinii\*\*\**, an isolate from *Ixodes persulratus* in the former Soviet Union. Differences in serum reactivity to various strains were noted for.

ORGN . . .

Chordata, Animalia; Leporidae: Lagomorpha, Mammalia, Vertebrata,  
Chordata, Animalia; Procyonidae: Carnivora, Mammalia, Vertebrata,  
Chordata, Animalia; Spirochaetaceae: Eubacteria, Bacteria

ORGN Organism Name

*\*\*\*Borrelia\*\*\* burgdorferi* (Spirochaetaceae); *Odocoileus virginianus* (Cervidae); *Peromyscus leucopus* (Cricetidae); *Procyon lotor* (Procyonidae); *Sylvilagus flordanus* (Leporidae)

ORGN Organism Superterms

animals; artiodactyls; bacteria; . . .

L15 ANSWER 20 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

8

AN 1995:453096 BIOSIS

DN PREV199598467396

TI Molecular analysis of a 66-kDa protein associated with the outer membrane of Lyme disease *\*\*\*Borrelia\*\*\**.

AU Bunikis, Jonas; Noppa, Laila; Bergstrom, Sven (1)

CS (1) Dep. Microbiol., Umea Univ., S-901 87 Umea Sweden

SO FEMS Microbiology Letters, (1995) Vol. 131, No. 2, pp. 139-145.

ISSN: 0378-1097.

DT Article

LA English

AB A 66-kDa protein (p66) associated with the outer membrane of Lyme disease *\*\*\*Borrelia\*\*\** was analysed at the molecular level. The chromosomal genes encoding p66 in *B. burgdorferi* B31, *B. afzelii* ACAI, and *B.*

*\*\*\*garinii\*\*\** *\*\*\*Ip90\*\*\** were sequenced. Database searches revealed that the p66 gene sequences were homologous to a previously reported gene fragment of unknown function. The deduced amino acid sequences of p66 in different Lyme disease *\*\*\*borreliae\*\*\** were 92-94% identical and had no homologs in the databases. Proteolytic cleavage patterns of p66 and a

computer-predicted single trans-membrane helix suggested the presence of surface-exposed epitopes on the C-terminus.

TI Molecular analysis of a 66-kDa protein associated with the outer membrane of Lyme disease \*\*\*Borrelia\*\*\*

AB A 66-kDa protein (p66) associated with the outer membrane of Lyme disease \*\*\*Borrelia\*\*\* was analysed at the molecular level. The chromosomal genes encoding p66 in *B. burgdorferi* B31, *B. afzelii* ACAI, and *B. garinii* \*\*\*Ip90\*\*\* were sequenced. Database searches revealed that the p66 gene sequences were homologous to a previously reported gene fragment of unknown function. The deduced amino acid sequences of p66 in different Lyme disease \*\*\*borreliae\*\*\* were 92-94% identical and had no homologs in the databases. Proteolytic cleavage patterns of p66 and a computer-predicted single trans-membrane. . .

IT Sequence Data  
amino acid sequence; molecular sequence data; nucleotide sequence;  
EMBL-X87725; EMBL-X87726; EMBL-X87727

IT Miscellaneous Descriptors  
LYME \*\*\*BORRELIOSIS\*\*\* ; OUTER MEMBRANE PROTEIN

ORGN Super Taxa  
Spirochaetaceae: Eubacteria, Bacteria

ORGN Organism Name  
\*\*\*Borrelia\*\*\* afzelii (Spirochaetaceae); \*\*\*Borrelia\*\*\*  
burgdorferi (Spirochaetaceae); \*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\*  
(Spirochaetaceae)

ORGN Organism Superterms  
bacteria; eubacteria; microorganisms

L15 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2002 ACS

AN 1995:397240 CAPLUS

DN 122:185342

TI Immunogenic formulation of OspC antigen vaccines for the prevention and treatment of Lyme disease and recombinant methods for the preparation of such antigens

IN Livey, Ian; Crowe, Brian; Dorner, Friedrich

PA Immuno AG, Austria

SO PCT Int. Appl., 104 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9425596	A2	19941110	WO 1994-EP1365	19940429
WO 9425596	A3	19941222		
			W: AT, AU, CA, CZ, FI, HU, JP, NO, PL, RU, SI, SK, US	
			RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE	
AU 9467229	A1	19941121	AU 1994-67229	19940429
AU 683260	B2	19971106		
EP 701612	A1	19960320	EP 1994-915562	19940429
EP 701612	B1	19980121		
			R: AT, BE, CH, DE, DK, ES, FR, GB, IE, IT, LI, NL, PT, SE	
HU 72923	A2	19960628	HU 1995-2002	19940429
HU 217024	B	19991129		
JP 08509371	T2	19961008	JP 1994-523899	19940429
AT 162550	E	19980215	AT 1994-915562	19940429

ES 2114687 T3 19980601 ES 1994-915562 19940429  
SK 279968 B6 19990611 SK 1995-1341 19940429  
PL 178775 B1 20000630 PL 1994-311301 19940429  
FI 9505150 A 19951228 FI 1995-5150 19951027  
NO 9504318 A 19951229 NO 1995-4318 19951027  
PRAI US 1993-53863 A 19930429  
WO 1994-EP1365 W 19940429

AB Immunogenic formulations for protection against Lyme disease, use of the formulations for vaccination, OspC antigens, and a method for manuf. of OspC antigens with recombinant cells are claimed. An approach to \*\*\*Borrelia\*\*\* vaccine formulation taking into account serol., genotypic and epidemiol. information by which OspC proteins from different strains of *B. burgdorferi* are grouped together is described. OspC antigens are chosen in order to constitute a representative sample of such groupings, so that the resulting vaccine provides the greatest cross-protectivity with the fewest no. of antigens. Common membrane antigen type typing of *B. burgdorferi* strains, development of an OspC serovar typing scheme, RFLP anal. of ospC heterogeneity, and PCR amplification and sequencing of different alleles of the ospC gene and cluster anal. of the deduced amino acid sequences was described. Addnl., epitope mapping of anti-OspC monoclonal antibodies, cross-protection studies in gerbils, and frequency of occurrence geog. distribution of various families of OspC protein assocd. with human disease were presented. OspC antigens were produced with recombinant *Pichia pastoris*.

AB Immunogenic formulations for protection against Lyme disease, use of the formulations for vaccination, OspC antigens, and a method for manuf. of OspC antigens with recombinant cells are claimed. An approach to \*\*\*Borrelia\*\*\* vaccine formulation taking into account serol., genotypic and epidemiol. information by which OspC proteins from different strains of *B. burgdorferi* are grouped together is described. OspC antigens are chosen in order to constitute a representative sample of such groupings, so that the resulting vaccine provides the greatest cross-protectivity with the fewest no. of antigens. Common membrane antigen type typing of *B. burgdorferi* strains, development of an OspC serovar typing scheme, RFLP anal. of ospC heterogeneity, and PCR amplification and sequencing of different alleles of the ospC gene and cluster anal. of the deduced amino acid sequences was described. Addnl., epitope mapping of anti-OspC monoclonal antibodies, cross-protection studies in gerbils, and frequency of occurrence geog. distribution of various families of OspC protein assocd. with human disease were presented. OspC antigens were produced with recombinant *Pichia pastoris*.

ST OspC antigen \*\*\*Borrelia\*\*\* vaccine Lyme disease; sequence ospC gene antigen \*\*\*Borrelia\*\*\*

IT \*\*\*Borrelia\*\*\*

\*\*\*Borrelia\*\*\* afzelii  
\*\*\*Borrelia\*\*\* burgdorferi  
\*\*\*Borrelia\*\*\* \*\*\*garinii\*\*\*

#### Vaccines

(immunogenic formulation of OspC antigen vaccines for the prevention and treatment of Lyme disease and recombinant methods for the prepn. of such antigens)

IT 161377-94-2 161377-95-3 161377-96-4 161377-97-5 161377-98-6

161377-99-7 161378-00-3 161378-01-4 161378-02-5 161378-03-6

RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

( \*\*\*Borrelia\*\*\* OspC antigen fragment; immunogenic formulation of OspC antigen vaccines for the prevention and treatment of Lyme disease and recombinant methods for the prepn. of such antigens)

IT 146990-47-8, Protein pC ( \*\*\*Borrelia\*\*\* burgdorferi strain PKo gene pc reduced) 161630-06-4 161630-07-5, Protein ( \*\*\*Borrelia\*\*\* strain 2591 gene ospC) 161630-08-6, Protein ( \*\*\*Borrelia\*\*\* strain IP2 gene ospC) 161630-09-7 161630-10-0, Protein ( \*\*\*Borrelia\*\*\* strain ZS7 gene ospC) 161630-11-1, Protein ( \*\*\*Borrelia\*\*\* strain 297 gene ospC) 161630-12-2 161630-13-3, Protein ( \*\*\*Borrelia\*\*\* strain E61 gene ospC) 161630-14-4, Protein ( \*\*\*Borrelia\*\*\* strain ORTH gene ospC) 161630-15-5, Protein ( \*\*\*Borrelia\*\*\* strain ACA1 gene ospC) 161630-16-6, Protein ( \*\*\*Borrelia\*\*\* strain H9 gene ospC) 161630-17-7, Protein ( \*\*\*Borrelia\*\*\* strain J1 gene ospC) 161630-18-8 161630-19-9, Protein ( \*\*\*Borrelia\*\*\* strain M57 gene ospC) 161630-20-2, Protein ( \*\*\*Borrelia\*\*\* strain W gene ospC) 161630-21-3, Protein ( \*\*\*Borrelia\*\*\* strain VSDA gene ospC) 161630-22-4 161630-23-5 161630-24-6, Protein ( \*\*\*Borrelia\*\*\* strain KL10 gene ospC) 161630-25-7, Protein ( \*\*\*Borrelia\*\*\* strain \*\*\*IP90\*\*\* gene ospC) 161630-26-8 161630-27-9, Protein ( \*\*\*Borrelia\*\*\* strain BITS gene ospC) 161630-28-0, Protein ( \*\*\*Borrelia\*\*\* strain KL11 gene ospC) 161630-29-1, Protein ( \*\*\*Borrelia\*\*\* strain PB1 ospC) 161630-30-4, Protein ( \*\*\*Borrelia\*\*\* strain H13 gene ospC)

RL: PRP (Properties)

(amino acid sequence; immunogenic formulation of OspC antigen vaccines for the prevention and treatment of Lyme disease and recombinant methods for the prepn. of such antigens)